Strategies to improve adherence to active surveillance in lowintermediate risk prostate cancer

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Strategies to improve adherence to active surveillance in low-intermediate risk prostate cancer

Thesis presented in accordance with the requirements for the degree of Doctor of Philosophy

Translational Oncology and Urology Research (TOUR)

School of Cancer and Pharmaceutical Sciences

King's College London

United Kingdom

March 2019

A. Acknowledgement

When I qualified with a Diploma in Adult Nursing in '96', I didn't dare dream I might achieve what I have today. I do know that I could not have done this without the support of some very special people.

I would like to first thank a friend and prostate cancer patient 'Vincent Marren', who believed in me and my ability to achieve this award, leaving a research bequest in his will to further motivate me. Also to Lars Holmberg, who encouraged and supported my application for this PhD within his research group.

A huge thank you to Mieke Van Hemelrijck, who has proved generous, supportive and encouraging, giving above and beyond as both academic supervisor and friend. In addition, her family, Ruben and Finn who have provided both support and entertainment when needed most.

I would also like to thank my second supervisors; Declan Cahill for his unwavering support, enthusiasm and enduring 20 year friendship, and Christian Brown for his support and wise counsel throughout. I would also like to acknowledge my international collaborators: S. Carlsson, P. Stattin, A. Bill-Axelson and O. Bratt for offering the opportunity to work with and learn from them.

A big thank you to my closest friends, who have provided wide shoulders to lean on, (some for almost 40 years) and lots of positive encouragement when I struggled to believe in myself: Anya, Kathie and Chris, Ravi, JW, Lona, Clarissa, Penny and Ollie, Jane, Cat and Paul, Lorraine, Bill and Jean , Pete and Indy, Fahim and Peter.

And finally, a special thank you to my family: My husband Andrew, who has supported me without question through 7 years of Masters and PhD studies - the most fantastic project manager of our lives, My Mum, Sandy, Rich and families for being my cheering squad, and my adopted Irish family (special thanks to Carmel who kept her prayer candle lit throughout the writing up of this thesis) who kept in touch regularly to boost my spirits.

B. Abstract:

Background and aims

Despite support for active surveillance as a first treatment choice for men with low-risk prostate cancer, this strategy is largely underutilised and when chosen the drop-out rate is high (up to 38%) in the first 5 years (even where there is no evidence of cancer progression). In order to decrease the over treatment of men with low-risk prostate cancer it is important to understand the barriers and facilitators to active surveillance to consider in the design of future interventions to increase active surveillance choice and adherence.

Methods

A four stage modified Delphi technique was employed to achieve consensus on supportive care measures for active surveillance.

Stage 1 Data collection; a 5 year review of an active surveillance intervention aimed at active surveillance adherence, review of contemporary active surveillance cohorts worldwide, and a systematic review of the barriers and facilitators to active surveillance choice and adherence.

Stage 2 Qualitative study; semi-structured interviews with men who had opted out of surveillance without evidence of cancer progression

Stage 3 Data synthesis and Delphi survey; meta aggregation of qualitative and quantitative data from stages 1 and 2 to inform a two round patient and public involvement Delphi survey

Stage 4 Consensus; Expert active surveillance reference group consensus statements

Results

Key themes influence both choice and adherence to AS, which are interlinked in respect to experience: (1) cancer characteristics (tumour volume, grade, PSA marker); (2) patient factors (age, co-morbidities, knowledge, socioeconomic status, family history, fear of progression/side-effects); (3) family and social support; (4) provider (communication, attitudes, diagnostic experience); (5) healthcare organisation (administration, education, support) and (6) health policy (guidelines, awareness). Patients and healthcare professionals have different ideas concerning the priorities for active surveillance supportive care; however, the Active Surveillance Reference Group agreed 24 consensus statements for best practice in supportive care for active surveillance in respect of; (1) principles of an active surveillance programme; (2) structure of consultations; (3) content: Information and Support; (4) delivery of information.

Conclusion:

Many factors influence both men's choice and adherence to AS, with health care professionals prioritising different aspects of supportive care to those of patients. It is therefore essential to implement a robust patient and public consultation process during both the evidence acquisition phase as well as the design phase of future interventions aimed at increasing AS adherence.

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AS	Active Surveillance
ASRG	Active Surveillance Reference Group
BPH	Benign Prostatic Hyperplasia
BMI	Body Mass Index
DRE	Digital rectal examination
ERSPC	European randomized study of screening for prostate cancer
EUA	European Urology Association
HRQoL	Health related quality of life
LRPC	Low-risk prostate cancer
MRI	Magnetic Resonance Imaging
PC	Prostate cancer
PPI	Patient and Public Involvement
PRIAS	Prostate Cancer Research International Active Surveillance
PSA	Prostate-specific Antigen
PSAD	PSA density
PSADT	PSA doubling time
PSAV	PSA velocity
RALRP	Robot-assisted laparoscopic radical prostatectomy
SD	Standard Deviation
SEER	United States of America Surveillance, Epidemiology and End Results program 13
UK	United Kingdom
US	United States
WW	Watchful waiting

1. Chapter I. Introduction and research objectives

1.1. Introduction

Prostate cancer accounts for 400,000 new cancer cases in Europe (1) and 160,000 in the US (2) annually. Rapid uptake of prostate specific antigen (PSA) testing and better diagnostic procedures have led to a significant stage migration with earlier diagnosis of localised, low-risk prostate cancer (LRPC), ranging from 10% - 80% of all men diagnosed with prostate cancer worldwide (3-5) . The current European guidelines suggest a large proportion of men diagnosed with prostate cancer do not require immediate radical treatment, but can be safely monitored long-term using blood tests, digital rectal examination, prostate biopsy and/or multi-parametric magnetic resonance imaging (MRI) - an approach known as active surveillance (5).

Yet, despite the potential to monitor LRPC long-term with very little risk of disease progression (<0.03% over 15 years) (6), uptake of active surveillance varies across countries and practices (7) and drop-out is reported to be as high as 38% - even where there is no evidence of disease progression (6).

Over the last 10 years, I have developed my knowledge, experience and skills in the management of prostate cancer and 'living with and beyond cancer', using any academic research opportunities to further my knowledge and understanding of this in respect to active surveillance adherence. As a result of this interest, and as the concept of "living with and beyond cancer" developed into a key issue in cancer care, I was employed as a Uro-Oncology Nurse Consultant to explore opportunities to establish supportive care and self-

care management in men with prostate cancer, in both the post treatment setting and with those on active surveillance. In this capacity, I have been actively involved in developing supportive care strategies for men with prostate cancer across both my hospital and regionally as urology pathway group chair for the West London cancer vanguard group.

1.2. Research Objectives

The complexity of the issues men on active surveillance face and our lack of understanding as healthcare professionals of the concepts associated with choice and adherence to active surveillance, are the key drivers for this study. Understanding and prioritising the barriers and facilitators to active surveillance provides means for future research themes to study interventions aimed at increasing both the uptake of and adherence to active surveillance. This PhD thesis therefore demonstrates an original contribution to our knowledge through the following research objectives:

(1) Identification and evaluation of the barriers and facilitators for selection and adherence to active surveillance in low to intermediate risk prostate cancer through a systematic review of the current literature (up to March 2018).
(2) Exploration of the motivations of men who had dropped out of active surveillance (without evidence of disease progression) using a semi-structured interview technique.
(3) Prioritise patient and partner and healthcare professional supportive care needs on active surveillance using a modified Delphi approach. Review the level of concordance between healthcare professional views, patients and their partners.
(4) Achieve consensus of opinion on supportive care needs for men on active surveillance through an expert Active Surveillance Reference Group

Chapter II provides the relevant contextual information, including an overview of prostate cancer, diagnosis and prostate cancer epidemiology with a specific focus on active surveillance, whilst chapter III presents the methodology and methods used during this study.

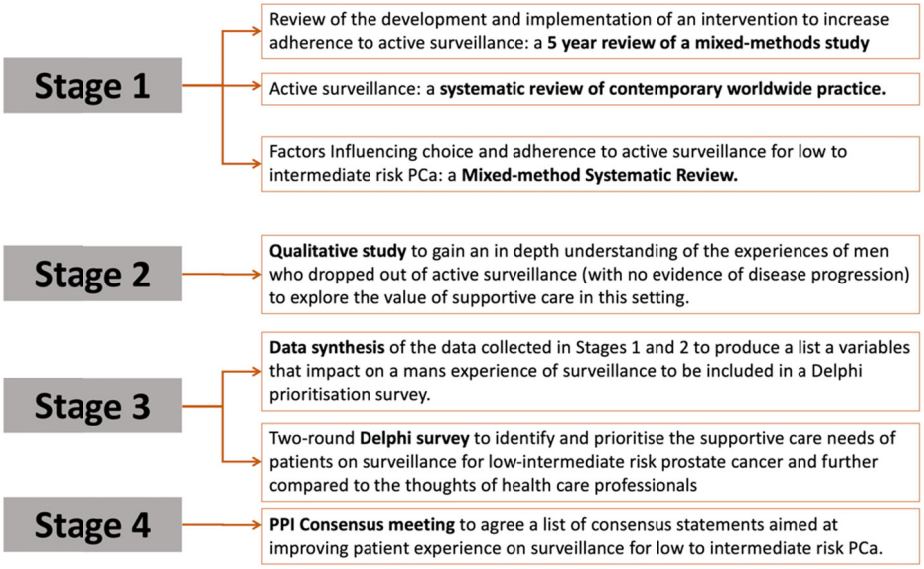
Chapter IV is presented in three parts. Part I describes a 5 year review of an active surveillance intervention, which is the original motivation for this thesis. Part II illustrates the current active surveillance scientific literature as a systematic review, focused on the barriers and facilitators of long-term active surveillance, and Part III explores the views of men who dropped out of active surveillance (without evidence of disease progression) in qualitative interviews.

Chapter V, presents a synthesis of these results (systematic review and qualitative interviews), and then describes a modified Delphi approach used to prioritise patient and partner needs on active surveillance comparing these results to those identified and prioritised by healthcare professionals.

Chapter VI, interprets the results and implications for practice, providing consensus statements developed through an expert Active Surveillance Reference Group. And finally, chapter VII provides a focus for future research.

This thesis, therefore, aims to provide insight into the supportive care priorities of men (and their partners) whilst on active surveillance. An applied research method employing a modified Delphi technique has been used to examine the current literature in addition to qualitative interviews to prioritise facilitators that increase adherence to long-term active surveillance in low to intermediate risk prostate cancer. More specifically, this thesis comprises of the following four stages:

Figure 1 *Four stages of thesis*



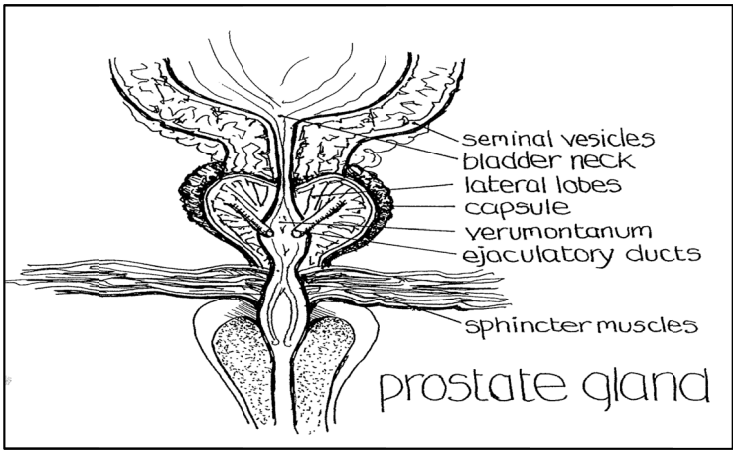
2. Chapter II Background

This chapter introduces the relevant contextual information, including an overview of the significance of prostate cancer and active surveillance.

2.1. The Prostate

Prostate cancer originates in the prostate gland of the male reproductive system. The term prostate was first attributed to Herophilus of Alexandria in 335BC, deriving from the Greek word *prohistani* that means, *'to stand in front of'*, used to describe the organs found in front of the bladder (8.). However, detailed descriptions of the anatomy of the prostate did not appear until the Renaissance (1400-1600AD). The development of the prostate gland (Figure 2) begins following the testosterone surge of puberty.

Figure 2 Prostate gland and surrounding structures



Reproduced with kind permission from an image by Richard Henry (2014)

In the normal adult its size and shape resembles that of a walnut, 3cm in length, 4cm in width and 2cm in depth. It sits just in front of the rectum, between the bladder and the penis, surrounding the urethra that takes a curved path through the gland ending close to the anterior surface of the prostate. The prostate secretes fluid that nourishes and protects sperm, expelled at ejaculation to become semen. Current thinking suggests that the nerves

responsible for ejaculation are posterior to the neurovascular bundle that forms part of a hammock of nerves in which the prostate lies (9).

The gland itself is partly muscular and partly glandular, has four distinct zones (transitional, central, peripheral and anterior fibromuscular stroma) and is made up of ducts and alveoli lined by columnar epithelium (9). Ninety per cent of prostate cancers are adenocarcinomas formed in the glandular cells of the prostate; the remaining ten per cent are made up of a range of rare tumour types (9). Although cancer of the prostate can spread to other parts of the body, it is generally considered to be a slow growing or indolent cancer. However, conditions of, and treatment to, the prostate have the potential to affect its function and that of adjacent organs, potentially affecting bladder, bowel, penile and sexual function.

2.2. Risks and causes

Age is the most significant risk factor for prostate cancer. Men aged under 50 years have a very low risk of developing the disease, but the risk subsequently increases with age and in the UK about 70 per cent of all cases are diagnosed in men over 65 years of age (1). There is evidence for some familial genetic component to prostate cancer: men with a first-degree relative (father, brother) who has had the disease are two to three times more likely to develop it (10). West African men and black men from the Caribbean are also at increased risk of developing the disease compared to white men, and Asian men have the lowest risk. Although obesity may affect the risk of developing prostate cancer, currently no definitive modifiable risk factors have been identified (11).

2.3. Diagnosis

Diagnosing prostate cancer is not straightforward, involving many areas of uncertainty. Screening for prostate cancer is also controversial. Although testing for Prostate Specific Antigen (PSA) involves a relatively simple blood test, the results are not easy to interpret; a raised PSA may be the result of a benign condition, prostate infection or inflammation or urinary infection. It may not be raised even if prostate cancer is present and any cancer detected may be very slow growing, only impacting on anxiety or unnecessary treatment (11). In a recently published European study of over 13,000 men, a sustainable reduction in prostate cancer death attributable to PSA testing was demonstrated, but the author's caution on the need to assess potential harm before any recommendation on population-based screening is made (12). As a result of this uncertainty, there is currently no organised screening programme for prostate cancer in the UK, instead Public Health England provides an informed choice programme, Prostate Cancer Risk Management (11) which is administered by general practitioners.

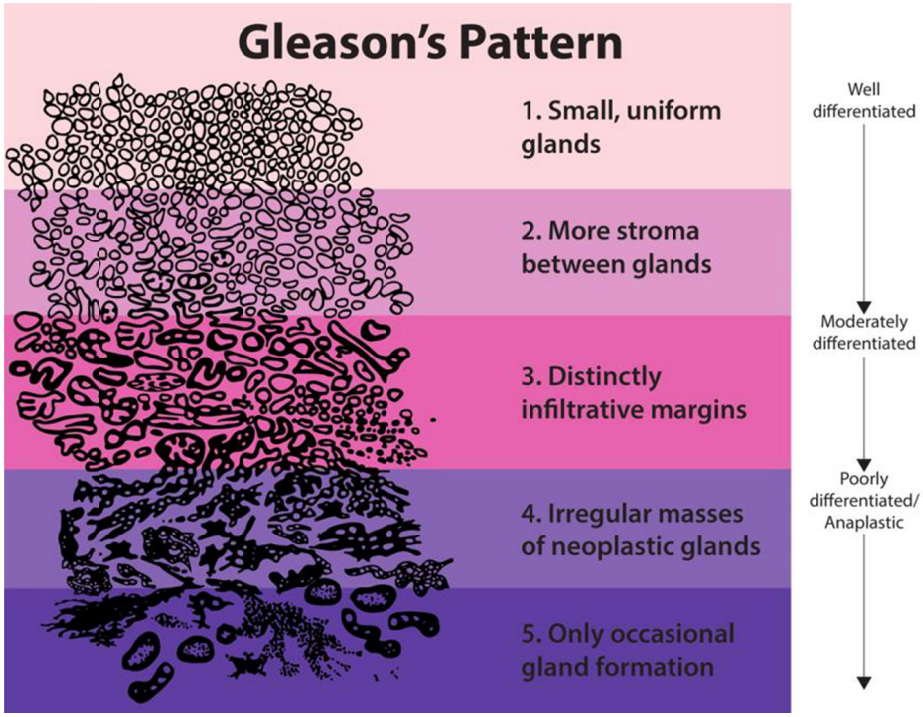
The majority of prostate cancer cases are detected as a result of PSA testing and very few from the presentation of specific symptoms. In the event of a raised PSA or symptoms of pressure on the urethra, a digital rectal examination (DRE) can assess if the prostate is enlarged or irregular and forms an essential part of the diagnosis. Most recently, as a result of the Department of Health sponsored multi-centre Prostate MRI Imaging Study (PROMIS), which demonstrated that 27% of patients would avoid a primary biopsy and that 5% fewer clinically insignificant prostate cancers would be diagnosed (13), there has been a paradigm shift in the way men with suspected prostate cancer are investigated. The new National

Institute of Clinical Excellence guidelines currently out for consultation (December 2018) inserted Magnetic resonance imaging (MRI) into the diagnostic pathway as a pre-biopsy tool for both targeting suspicious lesions and potentially ruling out the need for invasive biopsies (14). Up until now, biopsy has been carried out without the benefit of directive imaging and the incidence of false negative biopsies is reported as significant (9).

Pathological diagnosis is usually made by a combination of architectural and cytological features of the biopsy sample that defines the grade of the cancer. This refers to the degree of differentiation in the cell as seen under the microscope (15). Cancers that closely resemble the original or normal tissue of the prostate are considered well-differentiated or low grade, whereas those that vary notably from the original are considered poorly differentiated or high grade (9).

In the 1960s, Dr Donald Gleason developed the grading system that is almost universally used today. The cancer is graded based on the growth pattern and degree of differentiation of the biopsy sample on a scale of 1 (most differentiated) to 5 (least differentiated) (16). However, more than one sample will be taken at the time of the biopsy because there may be areas of differing grades within the tumour. The Gleason score is then calculated by adding together the most prevalent and the second most prevalent grades to give an average rather than the worst or the best (Figure 3 - (16)).

Figure 3 Gleason's pattern



The higher the Gleason score, the greater the risk that the cancer has, or could spread. Tumour volume is another significant prognostic factor and men with high-risk indicators will be assessed to establish the extent to which the disease has spread outside the prostate, to the regional lymph nodes or beyond (9). The final diagnosis of prostate cancer then receives a universal classification for tumour, node and metastatic (TNM) involvement which was updated in 1992 (17). However, in 2016 a new grading system for prostate cancer was developed by Epstein and colleagues (15) (Table 1) with the obvious benefits of:

1) More accurate grade stratification than the current Gleason system

2) Simplified grading system of 5 as opposed to multiple possible scores depending on various Gleason pattern combinations

3) Lowest grade is 1 as opposed to current practice of Gleason score 6, with the potential to reduce overtreatment of indolent prostate cancer

Table 1 Gleason grade group – Gleason score

Grade Group	Gleason score	Description
1	3 + 3 = 6	Only individual discrete well-formed glands
2	3 + 4 = 7	Predominantly well-formed glands with lesser component of poorly formed/fused/cribriform glands
3	4 + 3 = 7	Predominantly poorly formed/ fused/cribriform glands with lesser component of well-formed glands*.
4	8	Only poorly formed/fused/cribriform glands or - Predominantly well-formed glands and lesser component lacking glands ** - Predominantly lacking glands and lesser component of well-formed glands **
5	9–10	Lack of gland formation (or with necrosis) with or without poorly formed/fused/cribriform glands*

*For cases with >95% poorly formed/fused/cribriform glands or lack of glands on a core or at radical prostatectomy, the component of <5% well- formed glands is not factored into the grade. ** Poorly formed/fused/cribriform glands can be a more minor component.

2.4. Treatment and follow-up

Treatment decisions for localised prostate cancer are based on the likelihood that the cancer will progress at a rate that will affect the individual, balanced against the potential harm of treatment. Common treatment options include surgery, radiotherapy (external beam and brachytherapy), hormone therapy, cryotherapy and High Intensity Focused Ultrasound (HIFU). There is no gold standard treatment and some treatments are currently only available as part of clinical research or in a designated number of cancer centres (18). A large percentage of prostate cancers diagnosed are now categorised as of no clinical significance where active surveillance is recommended (12) . Surveillance includes regular prostate specific antigen (PSA) blood test monitoring, prostate biopsies and magnetic resonance

imaging (MRI). Growth in the tumour volume or upgrading of the Gleason score will trigger treatment (18).

The clinical follow-up of men treated for localised prostate cancer in the UK has followed the traditional medical model of gradual reduction in attendance, but with no defined end point and this model has evolved over many years with no tangible evidence base. In the example of prostate cancer, the National Institute of Clinical Excellence Guidelines (19) suggest PSA levels are checked six weeks after completion of treatment, every three to six months for at least two years then reduced to annually potentially *ad infinitum*.

This *status quo* was challenged in 2014 with the introduction of a proposal for stratified pathways of follow-up calculated on disease and individual risk factors that questions the rationale for continuous follow-up in the face of no evidence (20). This, along with the more recent emphasis on the patient, the structure, delivery and economics of services have changed the way in which clinicians involved in the delivery of follow-up are challenging the cultural norms to improving patient experience.

2.5. Prostate cancer statistics

Prostate cancer is the second most common cancer diagnosis and the fifth leading cause of cancer mortality in men (21). In 2012, 1.09 million men were diagnosed worldwide, thus representing a substantial public health burden. In the UK this represents about 45,406 men, about 12 to 14 per cent of the total cancer incidence (1). Incidence rates have more than tripled over the last 35 years, but this is probably linked to the increasing use of Prostate

Specific Antigen (PSA) testing (22). Prostate Specific Antigen, a protein produced by the prostate gland and used as a blood marker for prostate cancer screening, has had a significant effect upon incidence by diagnosing cancers that would otherwise have remained undetected.

2.6. Active Surveillance epidemiology

The use of prostate specific antigen (PSA) testing and improvements in diagnostic procedures such as imaging and ultrasound guided biopsy have led to a significant increase in early diagnosis of localized, low-risk prostate cancer (LRPC), ranging from 10% - 80% of all men diagnosed with prostate cancer worldwide (21), and a subsequent decrease in prostate cancer mortality (3-5).

A substantial proportion of men with LRPC do not need treatment with surgery or radiation, but can be carefully monitored - an approach known as active surveillance. Overtreatment of LRPC is of concern, not only because of the physical and psychological morbidity associated with radical treatment, but also because of the economic healthcare burden (23, 24). Active surveillance is considered a safe alternative to immediate treatment and is endorsed by national medical organizations and guideline groups as a viable management option for men with LRPC (25).

More specifically, active surveillance for LRPC can be defined as a treatment strategy of close monitoring through blood tests (PSA), digital rectal examination, imaging and prostate biopsy, with conversion to curative treatment if progression occurs (26, 27). Large cohort

studies have shown that with appropriate patient selection, risk of dying from prostate cancer in men on active surveillance is low: 0.1% to 5.7% over 10 – 15 years (Appendix 8).

However, inconsistency in selection and adherence to active surveillance remains. Studies suggest that patient preference (28, 29), physician (30, 31), family and peer group influence (32, 33), national guidelines (34, 35) and local practices (36, 37) all influence this process. There is also no doubt that anxiety surrounding disease progression plays a significant role (38-40) in influencing long-term active surveillance adherence. It is reported that cancer continues to cause more fear than debt, knife crime, Alzheimer's disease and unemployment (41). Unsurprisingly therefore, studies continue to report that 1.6 to 38% of men opt out of AS often with no or little evidence of disease progression within five years (Appendix 8). Most recently, Movember's Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) database (10 296 men on active surveillance from 21 centres across 12 countries), reported on the reasons for active surveillance discontinuation.

At 5 years of follow-up, 27.5% (95% confidence interval [CI]: 26.4–28.6%) men showed signs of disease progression, 12.8% (95% CI: 12.0–13.6%) converted to active treatment without evidence of progression, 1.7% (95% CI: 1.5–2.0%) continued to watchful waiting, and 1.7% (95% CI: 1.4–2.1%) died from other causes. Of the 7049 men who remained on AS, 2339 had follow-up for >5 years, 4561 had follow-up for <5 years, and 149 were lost to follow-up. Cumulative incidence of progression was 27.5% (95% CI: 26.4–28.6%) at 5 years and 38.2% (95% CI: 36.7–39.9%) at 10 years (42).

However, in the last 10 years a trend towards active surveillance adoption in LRPC has been reported by many large database studies, with some variation still noted between countries, practices and physicians (7). Most notable are the upward trends seen in North America, Australia and Europe. In 2015, Cooperberg and Carroll reviewed US trends in active surveillance reporting from the US CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database. This demonstrated a sharp rise in the uptake of active surveillance, from 10% over the past twenty years to 40% in 2010-2013 (5). This was replicated in Europe with the Swedish National PC Register reporting a rise from 40% to 74% between 2009 and 2014 (35) and in Australia, where the Victorian PC Registry (43) reported a 16% rise in AS uptake between the first half of 2010 and second half (23.9% to 39.7%). This level (39%) was maintained over the following two years further increasing in 2015 up to 42.8% (44). This was also demonstrated in hospitals reporting on radical prostatectomy in both Canada and Germany. In Canada (Toronto), Louis and authors (45) reported a steady decline in the number of radical prostatectomies carried out for LRPC from 2007 (40.6%) to 2012 (13.6%), whilst in Germany the Martini Clinic (46) demonstrated a similar decrease for low-risk Gleason score 6 cancer in 2014 (12.1%) in comparison to 52.2% in 2000.

However, this increase is not universal. In contrast, a 2014 survey (47) of 2,133 Japanese urologists suggested that 26.9% reported no use of active surveillance for LRPC and another 50.6% reported using active surveillance in <5% of their patients. Moreover, only 27% of respondents indicated that they would want to offer active surveillance more frequently in the future.

3. Chapter III: Methodology: Applied research

3.1. Introduction

The following chapter presents the rationale for methodology used and methods chosen to address the question "What supportive care strategies are required to improve adherence to active surveillance in low-intermediate risk prostate cancer?"

In Part I of this chapter I present the theoretical underpinning of the research strategy used; Applied research, using a mixed methodology, and in Part II, I discuss the approach used to conduct this study; a modified Delphi method. Part III describes the methodological plan for this project.

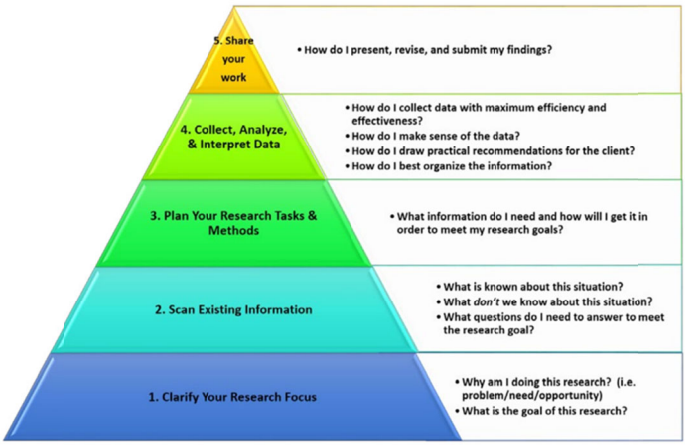
3.2. Part 1: Methodology

3.2.1. Applied research

The type of methodology adopted by any research project depends upon the central research objective and questions (48, 49). Applied research refers to the rigorous investigation conducted to answer a specific clinical question or solve a practice related-problem. The goal of applied research is to improve the human condition. It focuses on analysis and solving social and real life problems.

To achieve this aim a five-step framework is used in the applied research process (Figure 4).

Figure 4 Five-step framework for Applied research process.



Applied research is not limited to one particular stream of data collection and methodology. In fact, the use of mixed-methods not only provides a more in-depth data set but also allows the researcher to validate findings (50). Validity means the extent to which the study is credible, accurate and free of biases, and this criterion is met if the study actually does what it says it is doing, and the data adequately and accurately represents actual conditions. To meet this criterion, one has to make every effort to eliminate bias, distortion, and unsupported assumptions and conclusions from every step of the research. These threats can be found at any stage of the study – including in the definition/conceptualization, sampling, question formulation, data collection and analysis, and development of recommendations (51).

3.2.2. Mixed methods:

Over the last three decades mixed method research studies have been recognised as a valuable tool in health care (49, 52). In fact, the use of a mixed methodology in this project provides a more in-depth data set and also allows for validation of the findings to ultimately increase their reliability (50). Quantitative research was therefore used to answer the where,

what, who and when questions (48, 53). To explore the phenomenon (49, 53) of active surveillance adherence, I used qualitative research to provide the necessary in-depth view (54), which researchers argue provides a better basis for analysis and interpretation because it is grounded in the natural environment of the phenomenon (55).

The process of validation described above, is known as triangulation (49), where a variety of sources and methods are used in a study to further validate. Ritchie and Spencer (56) broke this process down into a four category framework to include: contextual, diagnostic, evaluative and strategic factors which I have further adapted in the context of this research question (Table 2).

Table 2 Categories of triangulation: contextual, diagnostic, evaluative and strategic

Category	Goal	Sample questions
Contextual	Identifying the form and nature of what exists in the active surveillance literature	What are the dimensions of attitudes/perceptions that are held? What is the nature of people's experiences? What needs do the population have? What elements operate within a system?
Diagnostic	Examining the reasons for, why men drop out of active surveillance	What factors underlie particular attitudes/perceptions? Why are decisions or actions taken, or not taken? Why do particular needs arise? Why services or programs are being/not been used?
Evaluative	Appraising the effectiveness of existing active surveillance interventions	How are objectives achieved? What affects the successful delivery of programme services? How do experiences affect subsequent behaviour? What barriers exist to current operating systems?
Strategic	Identifying and developing new theories, plans or actions using a patient and public involvement strategy	What types of services are required to meet needs? What actions are needed to make program services more effective? How can systems be improved? What strategies are required to overcome the defined problems?

Adapted from "Qualitative data analysis for applied policy research" by Jane Ritchie and Liz Spencer in A. Bryman and R. G. Burgess (eds.) “Analyzing qualitative data”, 1994, pp.173-194 (56).

3.2.3. Using framework analysis in a mixed methods study:

The use of a framework to combine and analyse difference data sources is appropriate as a tool in the context of this type of research for the following reasons:

- It's a dynamic process that allows for change or amendment throughout the process.
- It provides systematic methodical treatment of the data.
- Its comprehensive

Framework analysis is a flexible process allowing the user to either collect all the data and then analyse it or do data analysis during the collection process. In the analysis stage the gathered data is sifted, charted and sorted in accordance with key issues and themes. This involves a five step process (56): a) familiarisation; b) identifying a thematic framework; c) indexing; d) charting; e) mapping and interpretation

1) Familiarisation:

This refers to the process during which the researcher becomes familiarised with the data collected (in this case, the interviews and systematic review) and gains an overview of the collected data (56). Throughout this process the researcher becomes aware of key ideas and recurrent themes and makes a note of them.

2) Identifying a thematic framework:

This occurs after familiarisation when the researcher recognises emerging themes or issues in the data set. It is at this stage that the researcher allows the data to dictate the themes and issues. To achieve this end, notes are taken during the familiarisation stage. The key issues,

concepts and themes that were expressed by the participants or in the literature now form the basis of a thematic framework that can be used to filter and classify the data (56).

Devising and refining a thematic framework is not an automatic or mechanical process, but involves both logical and intuitive thinking. It involves making judgments about meaning, relevance and importance of issues, and about implicit connections between ideas. Ritchie and Spencer (56) stress that the thematic framework is only tentative and there are further chances of refining it at subsequent stages of analysis.

3) Indexing:

During this phase portions or sections of the data that correspond to a particular theme are identified and then this process is applied to all of the data gathered. A numerical system is often employed to index the text and annotated in the margin (56).

4) Charting:

The data that was indexed in the previous stage are now arranged in charts of the themes, by lifting the data from its original textual context and placing it in charts that consist of the headings and subheadings that were drawn during the thematic framework (56).

5) Mapping and interpretation:

This phase involves the analysis of the key characteristics as laid out in the charts. This analysis provides a schematic diagram of the event/phenomenon, thus guiding the researcher in their interpretation of the data set. It is at this point that the researcher is cognisant of the objectives of the analysis, which are: “defining concepts, mapping range and nature of phenomena, creating typologies, finding associations, providing explanations, and developing strategies” (56).

This method of analysis and synthesis was used to inform the Delphi survey content and is described further in the methodological plan (Part II).

3.3. Part II: The 'Delphi method'

3.3.1. Background

The Delphi technique, developed by Dalkey and Helmer at the Rand Corporation in the 1950s (57), is a widely used and accepted method for achieving convergence of opinion concerning real-world knowledge solicited from experts within certain topic areas. It is directed at problem-solving, idea-generation, or determining priorities (58).

Predicated on the rationale that, "two heads are better than one" ((57) p.15), the Delphi technique is designed as a group communication process that aims at conducting detailed examinations and discussions of a specific issue for the purpose of goal setting, policy investigation, or predicting the occurrence of future events (59, 60). Whereas common surveys try to identify "what is," the Delphi technique attempts to address "what could/should be" (61).

The Delphi process has been used in various fields of study such as program planning, needs assessment, policy determination, and resource utilisation to develop a full range of alternatives, explore or expose underlying assumptions, as well as correlate judgments on topics spanning a wide range of disciplines. Consensus methods are commonly used in health services literature (62).

Other notable characteristics inherent with using the Delphi technique are the ability to provide anonymity to respondents, a controlled feedback process, and the suitability of a variety of statistical analysis techniques to interpret the data (63, 64). These characteristics

are designed to offset the shortcomings of conventional means of pooling opinions obtained from a group interaction in the form of focus groups (i.e., influences of dominant individuals, noise, and group pressure for conformity) (65).

One of the primary characteristics and advantages of the Delphi process is subject anonymity, which can reduce the effects of dominant individuals - which often is a concern when using group-based processes used to collect and synthesise information (65).

Additionally, the issue of confidentiality is facilitated by geographic dispersion of the subjects, as well as the use of electronic communication, such as e-mail to solicit and exchange information. As such, certain downsides associated with group dynamics, like manipulation or coercion to conform or adopt a certain viewpoint ,can be minimised (66, 67).

3.3.2. What is the Delphi method?

Although there is considerable variation in how the Delphi method is applied, it has distinct characteristics:

1) it uses a group of participants (known as 'panellists') specially selected for their particular expertise on a topic.
2) it employs an initial 'idea generation' stage, in which panellists are asked to identify the range of salient issues.
3) it collates ideas from Round 1 to construct the survey instrument distributed in subsequent rounds.
4) it is often conducted across a series of two or more sequential questionnaires known as 'rounds'.

5) it has an evaluation phase (second or third round) where panellists are provided with the panel's responses and asked to re-evaluate their original responses.

6) it is interested in the formation or exploration of consensus, often defined as the number of panellists agreeing with each other on questionnaire items.

3.3.3. Delphi survey rounds:

Round 1: In the first round, the Delphi process traditionally begins with an open-ended questionnaire. The open-ended questionnaire serves as the cornerstone of soliciting specific information about a content area from the Delphi subjects (68). After receiving subjects' responses, investigators need to convert the collected information into a well-structured questionnaire. This questionnaire is used as the survey instrument for the second round of data collection. However, an acceptable and common modification of the Delphi process format is to use a structured questionnaire in Round 1 that is based upon an extensive review of the literature. Kerlinger (69) noted that the use of a modified Delphi process is appropriate if basic information concerning the target issue is available and usable.

Round 2: In the second round, each Delphi panellist receives a questionnaire that includes the items and ratings summarised by the investigators in the previous round and are asked to revise his/her judgments or "to specify the reasons for remaining outside the consensus" (70). This round gives Delphi panellists an opportunity to make further clarifications of both the information and their judgments of the relative importance of the items. However,

compared to the previous round, only a slight increase in the degree of consensus can be expected (71, 72).

3.3.4. Parameters for analysis

Decision rules must be established to assemble and organise the judgments and insights provided by Delphi subjects. However, the kind and type of criteria to use to both define and determine consensus in a Delphi study is subject to interpretation. Consensus can be decided if a certain percentage of the votes falls within a prescribed range (61). Ulschak recommended that consensus is achieved by having 80 percent of subjects' votes fall within two categories on a seven-point scale (73). Green (74) suggested that at least 70 percent of Delphi subjects need to rate three or higher on a four point Likert-type scale and the median has to be at 3.25 or higher. Scheibe and colleagues (75) advised that the use of percentage measures is inadequate. They suggested that a more reliable alternative is to measure the stability of subjects' responses in successive iterations. For the purposes of this project, we set out to follow Ulschak's (73) recommendation using a seven point Likert scale, however, few items achieved 80%, and therefore it was agreed by the Active Surveillance Reference Group that a 70% agreement rate was appropriate.

3.3.5. Selection of participants

Identifying appropriate subjects to participate in an expert reference group as part of a Delphi study, is the most important step in the process because it directly relates to the quality of the results generated (76). Since the Delphi technique focuses on eliciting expert

opinions over a short period of time, the selection of Delphi subjects is generally dependent upon the disciplinary areas of expertise required by the specific issue. There are no standards or exact criterion in the literature concerning the selection of Delphi participants, "throughout the Delphi literature, the definition of 'Delphi subjects' has remained ambiguous" (77). However, individuals are considered eligible to participate in a Delphi study if they have related backgrounds and experiences concerning the target issue, are capable of contributing, and are willing to revise initial or previous judgments for the purpose of reaching consensus (66, 78). In cases where patients are considered 'experts', a measurement of congruence can be employed, with the inclusion of healthcare professionals. Comparison between views can add to the Delphi method to determine levels of discordance/concordance (79) between patients and professionals views. This is of specific use in benchmarking current clinical thinking in anticipation of improving patient experience/services.

3.3.6. Power calculation

Ludwig (80) notes that the number of experts used in a Delphi study is "generally determined by the number required to constitute a representative pooling of judgments and the information processing capability of the research team" (p.52). However, what constitutes an optimal number of subjects in a Delphi study never reaches a consensus in the literature. Delbecq et al (81) recommended that researchers should use the minimally sufficient number of subjects and should seek to verify the results through follow-up explorations. They suggest that ten to fifteen experts could be sufficient if the background of the Delphi subjects

is homogeneous, whereas, Witkin and Altschuld (82) felt that heterogeneous Delphi panels (often found with expert patient panels) should generally include up to 50 participants.

3.3.7. Establishing an expert patient and public involvement (PPI) reference Group

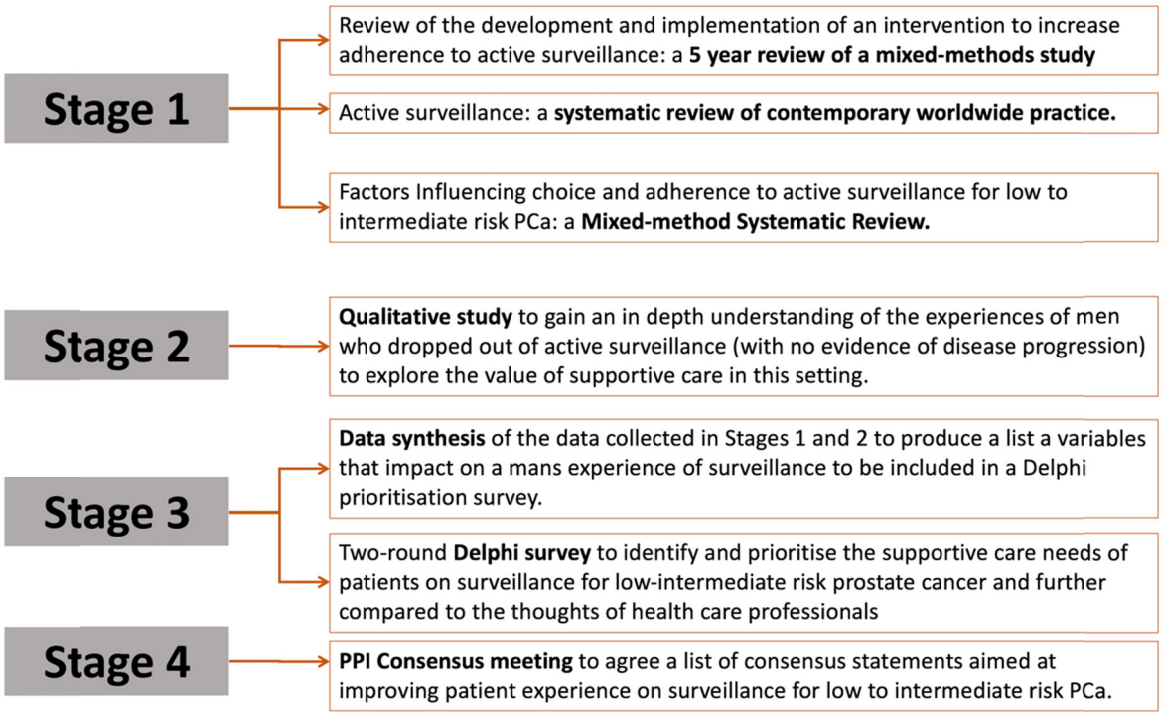
This project was based on the principles of PPI (83) research and as such key stakeholders including; men on active surveillance, healthcare professionals and the charitable sector were central to developing the initial research question and study design and forms the expert panel to achieve consensus in stage 4 of this study.

The expert Active Surveillance Reference Group (ASRG) was recruited from patients, partners, representatives (charitable sector) and health care professionals with a clinical interest in active surveillance. The group included 11 participants: four men on active surveillance, two men who had opted out of active surveillance despite no evidence of disease progression, two partners, one representative from the local BRC Patient and Public Involvement Group, two healthcare professionals and two representatives from local and national prostate charities. One third of the group were from black or ethnic minority groups, reflecting the local population. Initial discussions focused on the purpose, scope and structure of the proposed study, evidence presented from the systematic review as well as the important role of patient and public involvement in research. PPI initiatives were carried out 'with' members of the public rather than 'to', 'about' or 'for' them. In healthcare studies, the term public is interpreted broadly to include potential patients, carers, family, people who use health services, organisations that support users of health services and other interested members of the community (84).

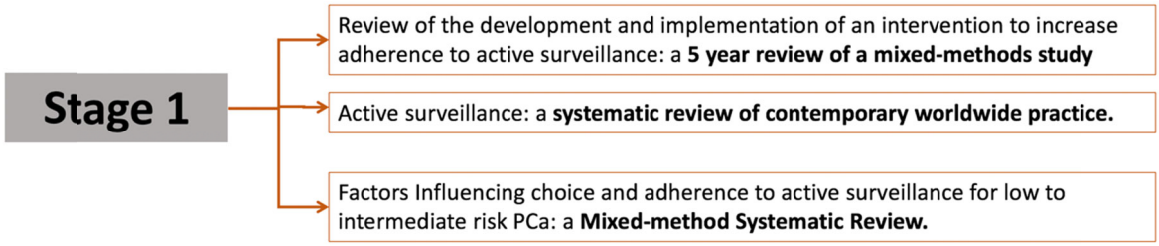
3.4. Part III: Methodological plan

A four-stage modified Delphi method was applied to the research question with the aim of achieving consensus between patients and healthcare professionals on the supportive care needs of men on long-term active surveillance to increase adherence. This modified approach consists of the following steps:

Figure 1 4 stages of study design



3.4.1. Stage 1 (Chapter IV)



3.4.1.1. Part I: A 5 year review of a mixed methods study

The protagonist for this thesis was a 5 year review of the treatment status of 255 consecutive men who were recruited to an intervention study in 2011. The aim of the intervention was to

increase adherence to active surveillance. Participants were allocated to either standard care (written information and access to a nurse specialist) or standard care and intervention (active surveillance education seminar).

Statistical analysis of outcome measures reviewed the proportion of men dropping out of AS for reasons other than disease progression, at 1 and 5 years from their prostate cancer diagnosis using multivariate logistic regression.

3.4.1.2. Part II: Systematic review of contemporary active surveillance practice

To explore any inequalities/differences in active surveillance protocols worldwide, Part II involved a systematic review of worldwide active surveillance practices in studies reporting ≥5 years of follow-up. I searched PubMed and Medline 2000-now and identified 13 AS cohorts.

Studies of interest were those describing baseline and clinical characteristics of the study population, and included; a patient selection criteria, monitoring/surveillance protocol, AS drop-out rates, triggers for conversion to radical treatment and outcomes during follow-up.

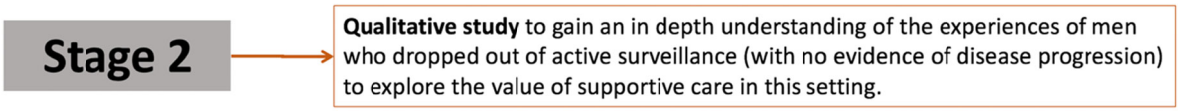
3.4.1.3. Part III: A mixed method systematic review

In Part III a mixed methods systematic review of the literature was carried out to explore and understand the barriers and facilitators to active surveillance choice and adherence in low to intermediate risk prostate cancer.

A modified version of The Joanna Briggs Institute – Methodology for JBI Mixed Methods Systematic reviews (Integrated approach) (85) was used to systematically review both

qualitative and quantitative data into a single mixed methods synthesis (85). A meta-aggregation of data was undertaken using a Bayesian approach, whereby all data was codified into themes and presented in a meta-aggregation through the generation of summative statements of the evidence to equally inform the topic in a mutually compatible format (86).

3.4.2. Stage 2: Qualitative study: Semi structured interviews (Chapter V)

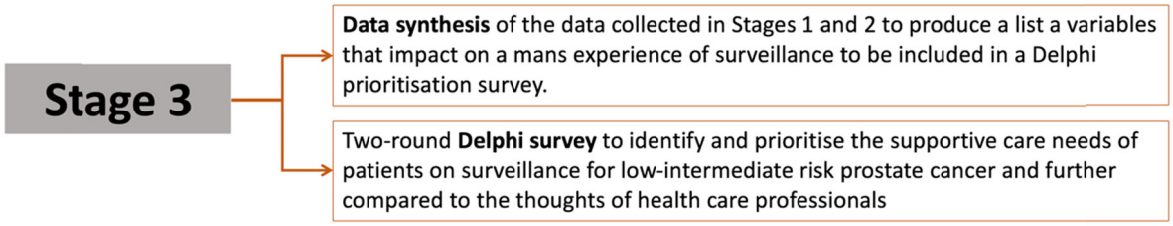


Stage 2, used a process of semi-structured interviews, where the questions were open ended, so as not to limit the respondents/interviewees choice of answers (87, 88). The purpose was to provide a setting/atmosphere where the interviewer and interviewee could discuss the topic in detail, with the interviewer making use of cues and prompts to help direct the interviewee into the topic area, to ensure a more detailed data set (88-90). The data collected in Stage 1 of this study was used to inform an initial interview topic guide for the interviews.

Patients were recruited through clinics at The Royal Marsden Hospital and King's College Hospital, as a patient and public involvement initiative, and a satellite prostate cancer clinic at Epsom and St Helier NHS Trust, authorised by The Royal Marsden Quality Improvement Project committee and Audit Lead at Epsom and St Helier NHS Trust.

As previously described, framework analysis was employed to determine themes amongst the interview data. This also provided focus as an easily repeatable procedure.

3.4.3. Stage 3: Data analysis and Delphi survey (Chapter VI)



3.4.3.1. Part 1: Data synthesis:

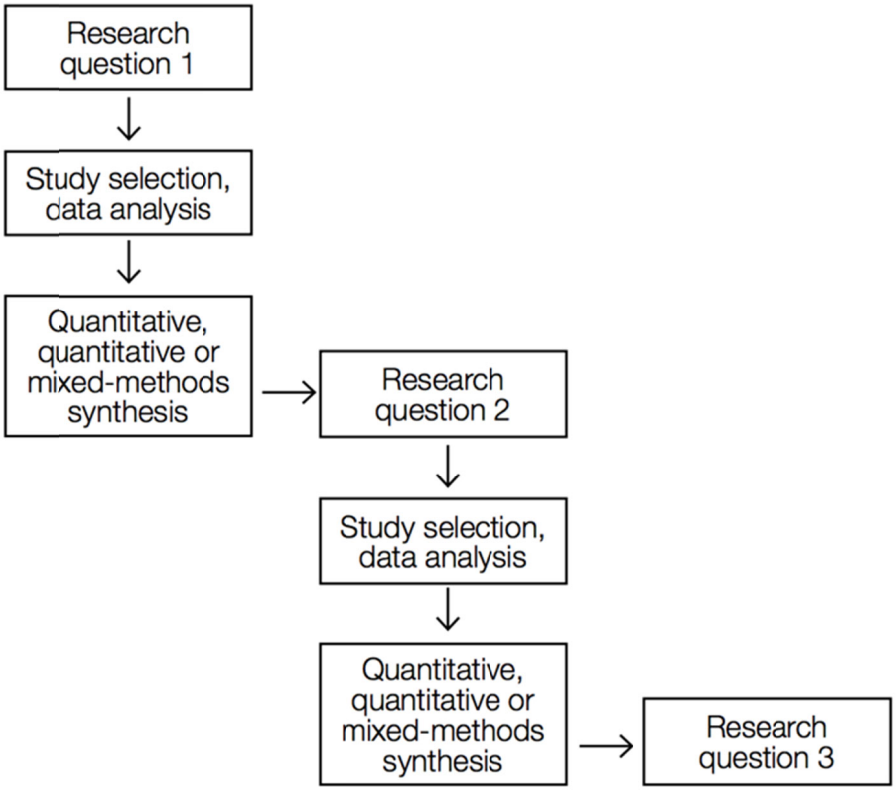
In Stage 3, I employed a framework analysis technique to analyse and synthesise the data collected in stages 1 and 2 of this study. This data synthesis would be used to inform the contents of the Delphi prioritisation survey.

Analysis of the data collected in stages 1 and 2 was carried out in accordance with The Joanna Briggs Institute contingent framework (85) (Figure 5). This framework involves two or more syntheses conducted sequentially based on results from the previous synthesis. This study began by asking a broad question "what factors influence choice and adherence to active surveillance" and is described in stage 1. This review subsequently generated a second research question, focused on the missing data from stage 1; to identify any differences in experience of men who had opted out of active surveillance without evidence of cancer progression (described in stage 2). Segregated synthesis was conducted for both research questions with the resulting synthesis presented as a set of themes/conclusions (86).

A bayesian method was then used to generate summative statements of the combined evidence through meta-aggregation. This was possible as all data collected during stages 1 and 2 had previously been translated into qualitative description statements thus permitting meta-aggregation in stage 3 (86) to inform the consensus items for the Delphi survey.

Figure 5 Conceptualisation of the mixed-method review process.

Adapted from Sandelowski et al. (2006) (86)



3.4.3.2. Part II: Delphi survey:

A two round Delphi prioritisation process aims to establish consensus and to score the supportive care requirements of men on active surveillance.

Although a traditional Delphi method consists of a group of experts producing items to be included in a Delphi-survey through an initial qualitative survey first round, in this study the scientific literature and interviews were strong and therefore items identified as barriers and facilitators to active surveillance in Stages 1 and 2, were used as survey items, with participants offered a free-text box to explore future or alternative thinking.

The expert Active Surveillance Reference Group met to discuss and agree the final Delphi survey items prior to distribution. The survey was then anonymised; however, some demographic information was collected, including: gender, age, relationship to patient (if not a patient), professional status, months on active surveillance. Healthcare professionals were asked for their age and professional qualifications. Patient participants provided an email address to be included in the second round of the prioritisation process; these were stored on the General Data Protection Regulation (GDPR) compliant smart survey website.

Patient and partner questionnaires were distributed through clinics as well as being sent to members of a local prostate cancer charity. The Healthcare professional survey was distributed via a snowballing technique shared through twitter. Two survey rounds were completed, as suggested for surveys where there is a clear literature base from which to establish the survey instrument (91).

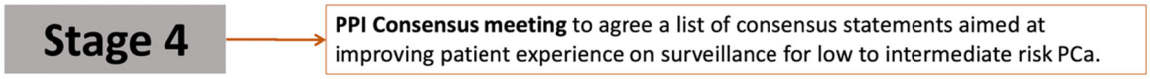
a) First -round Delphi prioritisation process

The first round of the survey included a list of items documenting the barriers and facilitators to active surveillance choice and adherence as defined in Part I. Participants were asked to score these items according to importance: 1 (not important) to 7 (most important). Participants were additionally provided with the opportunity to add additional suggestions for inclusion in a free text box.

b) Second-round Delphi prioritisation process

The second-round highlighted those questions which were ranked (>6) by 70% of the participants in the first round. It also included 10 newly identified suggestions from participants in round 1.

3.5. Stage 4: Stakeholder consensus meeting (Chapter VII)

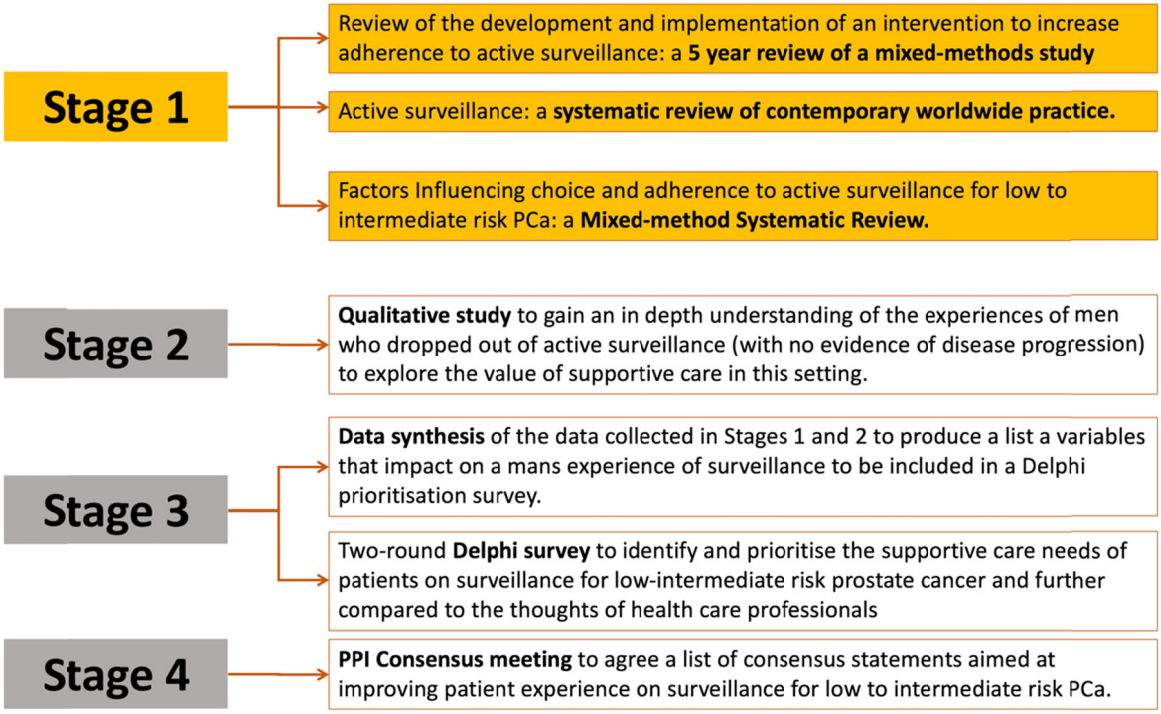


The expert Active Surveillance Reference Group was invited to participate in a face to face consensus meeting. The consensus meeting aimed for agreement on the identified supportive care priorities.

The highest scored priorities (70% of participants indicated a score of ≥6) were used to build the discussion for the consensus meeting. Stakeholders were asked to rank the supportive care priorities whilst on active surveillance for localised prostate cancer and provide their respective reasoning. Consensus statements were drafted on the basis of this discussion.

4. Chapter IV - Stage 1

This chapter is split into three parts and explores the rationale and background to this study. First, in Part I, I describe the protagonist for this thesis and explore long-term active surveillance adherence in the context of a previously implemented active surveillance intervention, Part II reviews contemporary active surveillance practices worldwide and lastly Part III provides context and background in a systematic review of the current scientific literature identifying the barriers and facilitators to active surveillance choice and adherence.



4.1. Part I: A 5 year review of an intervention to increase adherence to active surveillance

The findings of the following study were presented as an abstract at the European Association of Urology Annual Meeting in 2011 and 2018 and subsequently published in European Urology Oncology – September 2018 (Appendix 1) (92).

4.1.1. Introduction

As one of the first nurses in the UK specialising in prostate cancer diagnostics and the subsequent management of men with low-risk prostate cancer, I have developed within this emergent sub-speciality and became increasingly interested in the unique experience of 'living with and beyond cancer' and the supportive care aimed at the rising number of men who are monitored as part of an active surveillance programme.

European guidelines suggest a large proportion of men with localized, low risk prostate cancer (LRPC) do not require immediate treatment, but can be monitored – an approach known as active surveillance (93). However, as already mentioned international variation in determinants for safe active surveillance inclusion and follow-up (94) continue to contribute to high active surveillance drop-out rates (up to 38%) in men with no evidence of disease progression (6).

There are unique challenges represented in supporting men who have not been treated for localised prostate cancer, but have chosen active surveillance. These were only recently (2018) identified and categorised in my mixed-methods systematic review (95). The results of this review of active surveillance choice and adherence literature is outlined in chapter IV, but essentially reported six domains driving active surveillance drop-out: (1) patient characteristics; (2) tumour characteristics; (3) family and social support; (4) provider; (5) healthcare organisation; and (6) health policy. However, in 2009 when this project was initiated, little data existed detailing the specific concerns that men had relating to long-term active surveillance, studies at this time focused predominantly on informational interventions aimed at relieving the psychological anxiety related to side effects and long-term follow-up of

a treated population of men with prostate cancer. Oliffe (96) found that self-management strategies helped men cope with some of the long-term uncertainty of active surveillance, whilst 'The Prostate Cancer Lifestyle Trial' based on lifestyle modifications, including exercise and attention to stress management, demonstrated an improved treatment-free survival on active surveillance (97). Goh (98) found that men who perceived that they were receiving useful and consistent information were more satisfied with active surveillance and therefore more likely to continue on active surveillance whilst the UK-based ProtecT Trial (99) found merit in consistency of personnel to support and inform patients.

The following project review, outlines initial attempts to address the high level of active surveillance drop-out (@25%) (92) documented at a central/south-east London hospital based on needs identified by the local population. Here, I describe the development of the intervention; aimed at increasing active surveillance adherence and the results of the 5 year review undertaken. Completion of this project informed the direction of this thesis.

4.1.2. Patients and methods

This applied research project consisted of two parts: (1) Focus groups (FGs) to understand motivation and needs of men on active surveillance and to explore practicalities of an intervention to support active surveillance adherence; (2) Pilot intervention study to assess effect.

4.1.2.1. Focus groups

Permission was obtained from the local Urology audit committee to identify potential participants through electronic records (No: U13887). In December 2009 and April 2010, two FGs were facilitated by the Clinical Nurse Specialist (CNS) team. The first consisted of eight men who were currently on active surveillance and the second of seven men who had dropped out of active surveillance without evidence of progression. A semi-structured question guide was developed to provide structure for each FG (Appendix 2), based on a review of the available literature at this time (100).

We employed thematic analysis, an inductive process designed to identify and examine emerging themes from conceptual data (101). Thematic saturation in qualitative data has been reported at 15 (interview studies) (90) and therefore two FGs were scheduled. Purposive homogenous sampling was employed to provide conceptual significance to the question of adherence (102).

4.1.2.2. Developing the Intervention (Educational Seminar)

The intervention was developed in line with recommendations from the FGs.

A power-point presentation was co-authored by patients, nurses, and doctors with final ratification by the active surveillance reference group (4 partners of, and 10 men currently on or previously on AS).

The proposed 1.5 hour seminar included information on: imaging, biopsy techniques, understanding pathology, large AS cohorts - mortality and morbidity risk and diet and lifestyle advice. Optimal seminar delivery was defined as a team approach: urologist and CNS. Time was scheduled at the end of the seminar for questions and peer group discussion.

4.1.2.3. Recruitment

We employed a method of consecutive sampling (103) appropriate to a process of service improvement where a standard of care is evaluated both prior and after intervention. The inclusion criteria were men diagnosed with low-intermediate risk prostate cancer (as defined by the D'Amico classification system (104) Appendix 3), suitable for active surveillance based on information from Magnetic Resonance Imaging (MRI) and transrectal prostate biopsy with confirmatory transperineal prostate biopsy. The active surveillance progression criteria was, >G3+4 (transperineal biopsy approach - minimum 24 cores) or where the maximum contiguous cancer length was ≥6mm, >MRI - T2b, ≥30% of cores positive. Follow-up was carried out according to NICE guidelines (Appendix 4).

Between January 2011 and June 2011, 135 men were recruited (Group A), and offered standard care (NICE (19): introduction to a CNS and written information on active surveillance (PCUK (105)). A second consecutive group recruited between July 2011 and December 2011 (Group B) included 120 men who were offered standard care and participation in the educational seminar.

This study compared active surveillance drop-out rates at 1 and 5 years post diagnosis. Patient and clinical characteristics at diagnosis, and outcomes were compared between both groups using descriptive statistics. Multivariate logistic regression, adjusted for age, grade, diagnostic PSA, digital rectal examination and clinical stage, examined whether differences in drop-out rates were independent of patient characteristics.

4.2. Results

4.2.1. Qualitative analysis

4.2.1.1. Designing the intervention: FGs

The themes emerging from the two FGs were (1) consistency in clinical team, administration and follow-up protocol, (2) consistent information re: prostate cancer and active surveillance, and (3) diet and lifestyle advice.

1) Clinical consistency (Appendix 5 Panels 1 & 2)

In both FGs, men described importance of a consistent approach to follow-up as well as familiarity with the clinical team.

Men still on active surveillance found reassurance: “my CNS always sees me for my PSA review, I have a great relationship with her, I could ask her anything”.

Men in the group that had dropped out of active surveillance described their experience as stressful: “*nobody could give me any guarantees about AS follow-up, every guideline seemed to be different. It made me very nervous*”. They also described inconsistencies in the clinical team as: “*very difficult”*.

2) Consistent information (Appendix 5 panels 3 & 4)

The two FGs differed in their response to the information given during active surveillance. Those who had remained on active surveillance felt that the amount of information given was adequate: "*I was given some information leaflets by my CNS. I thought they were very good*". The men who had dropped out of active surveillance described the information as inconsistent: "*every time I saw a new doctor or nurse I would question them about PC and AS. Sometimes the answers were the same, other times they sounded like they didn't know what they were talking about*".

3) Diet and lifestyle advice (Appendix 5 panels 5 & 6)

Men remaining on active surveillance described self-help as a major contributor to their quality of life. "I found lots of information on the internet about diet and exercise. I changed my diet and began to go to the gym. I think everyone who has cancer should be aware. I've never felt better".

Men who had opted out of active surveillance suggested that: "there really wasn't any information on how I might help myself on active surveillance" and "I don't think the nurses or doctors believed that diet, exercise or complimentary treatments would help on active surveillance. I might have stayed on active surveillance if I'd had the opportunity to discuss this".

4.2.1.2. Developing the intervention

The FGs discussed the medium through which the information and support should be given: website, bespoke written information, webinar and peer-group seminar. Men who had dropped out of active surveillance described their experience of websites and on-line forums as "*cold*". The men who had remained on active surveillance, felt that websites gave no opportunity for feedback and that the forums, although interactive in some cases, were "*extreme and unpoliced*". There was universal agreement that the content of the intervention should be empowering, with an emphasis on self-care. Thirteen of fifteen participants agreed that a peer group one-off educational seminar would suit the needs of the majority, with an option to re-attend when/if required. The seminar was suggested to be held within three months of choosing active surveillance to mirror the early support and information that men undergoing radical treatment received.

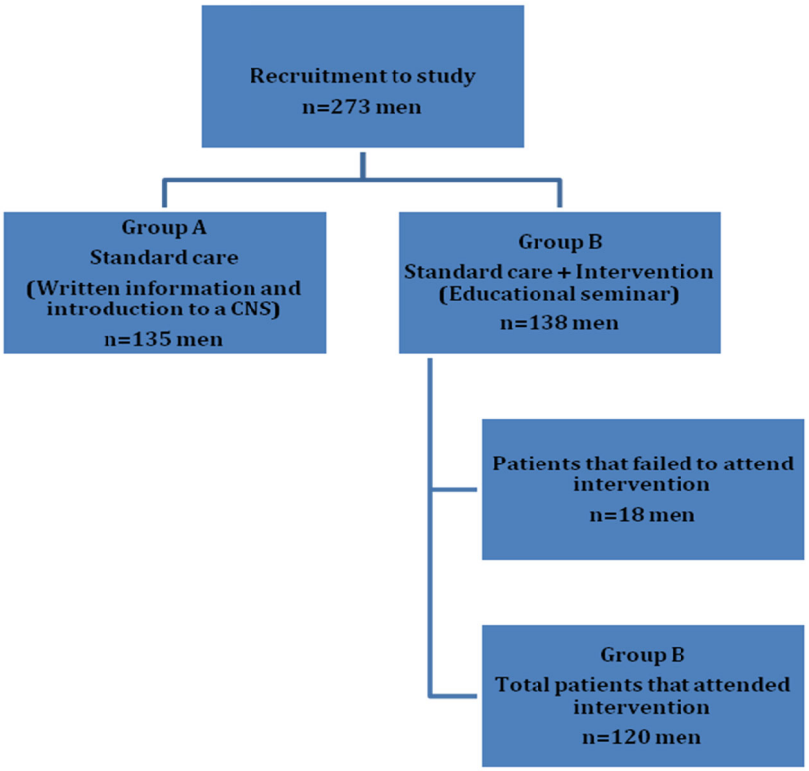
It was also suggested that the content of the seminar had to be similar to our program of seminars offered to men undergoing prostatectomy and radiotherapy (92). Five topics were agreed on: Imaging, biopsy techniques, pathology, mortality and morbidity risk in active surveillance and dietary and lifestyle advice.

4.2.2. Quantitative analysis

4.2.2.1. Patient demographics

273 men were recruited to the study. 18 men in the intervention group failed to attend the seminar and were therefore omitted from the final analysis. This left 255 men, 135 in group A and 120 in group B (Figure 6).

Figure 6 Recruitment to study



No statistically significant differences were found between the two groups for age, PSA and DRE clinical stage at study entry (Table 3).

Table 3 Patient characteristics and adherence of study participants in both arms of the non-randomised intervention study.

Characteristics at active surveillance entry	Standard Care (Group A)	Educational Seminar (Group B)
	n=135	n=120
Mean Age (SD)	62.4 (6.8)	63.3 (7.4)
Mean PSA (SD)	9.2 (7.0)	8.6 (5.3)
	n (%)	n (%)
Grade		
3+3	42 (31.1)	111 (92.5)
3+4	93 (68.9)	9 (7.5)
DRE assessment		
Benign	47 (34.8)	46 (38.3)
T2	77 (57.0)	68 (56.7)
T3	11 (8.2)	6 (5.0)

A statistically significant difference was, however, found in relation to Gleason grade group (GGG): 42 men (31%) in group A compared to 111 (93%) in group B with GGG1. 93 men (69%) in group A and 9 men (7%) in group B were diagnosed with GGG2. This was felt to be most likely associated with an increase in confidence for local active surveillance monitoring practice in the intermediate prostate cancer risk group (106).

4.2.2.2. Adherence to active surveillance

No men demonstrated clinical disease progression in the first year. However, 25% of group A compared to 11% in group B did drop out of AS (Table 4) (p=0.003).

Table 4 Active surveillance outcomes based on intervention group at 1 and 5 years.

Program outcomes	Standard Care (Group A)	Educational Seminar (Group B)	p-value
At 1 year:			
Remained in active surveillance program	101 (74.8)	107 (89.2)	
Dropped out due to disease progression	0	0	
Dropped out with no disease progression	34 (25.2)	13 (11.2)	0.003
At 5 years:			
Remained in active surveillance program	62 (45.9)	68 (56.7)	
Dropped out due to disease progression	17 (12.6)	26 (21.7)	
Dropped out with no disease progression	56 (41.5)	26 (21.7)	<0.001

By year 5, patients in group B remained less likely to drop out of active surveillance. Drop-out without evidence of progression was 21.7% in group B compared to 41.5% in group A (p<0.001) (Table 4). Due to the difference in clinical characteristics between the two groups,

at 5 years following diagnosis the active surveillance drop-out rate due to cancer progression was higher in group B than in group A, 21.7% versus 12.6% (107, 108).

Drop-out rates remained significantly lower among seminar participants, after adjustment for baseline clinical characteristics, including GGG, at both 1 year (OR = 0.21, 95% CI 0.09-0.49) and 5 years (OR=0.26, 95% CI 0.12-0.56) (Table 5). Identical results were found when restricting the analysis to GGG1 with an odds ratio of 0.25 (0.11-0.53) for drop out in patients without evidence of disease progression at 5 years (Table 5).

Table 5 Multivariate logistic regression for odds of dropout for reasons other than disease progression

All models were adjusted for age, grade, diagnostic PSA, digital rectal examination and clinical stage.

Patient characteristics (at entry into AS)	At 1 year n=253	By 5 years (whole cohort) n=253	By 5 years (excl. men with disease progression) n= 210
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Educational seminar			
no	1.00	1.00	1.00
yes	0.21 (0.09-0.49)	0.25 (0.12-0.51)	0.26 (0.12-0.56)
Age (continuous)	1.03 (0.98-1.09)	0.94 (0.91-0.98)	0.93 (0.90-0.98)
PSA (continuous)	0.94 (0.88- 1.01)	0.96 (0.52-1.01)	0.98 (0.93-1.04)
Gleason Grade Group			
GGG1	1.00	1.00	1.00
GGG2	0.44 (0.20-0.97)	0.49 (0.23-1.00)	0.48 (0.22-1.02)
DRE			
Benign	1.0	1.00	1.00
T2	0.88 (0.43-1.79)	0.98 (0.54-1.77)	0.93 (0.50-1.72)
T3	1.42 (0.41-4.91)	1.69 (0.54-5.32)	3.88 (0.96-15.7)

4.2.3. Discussion

This is the first mixed methods study to develop and assess impact of an educational/supportive intervention on active surveillance adherence over a five year period. Our findings demonstrated effectiveness of a structured, interactive, educational seminar in increasing adherence to active surveillance for men with low-intermediate risk prostate cancer.

The needs of men requiring radical treatments for prostate cancer have been examined previously and have helped to define and develop the role of the CNS in supporting patients (109). However, less is known about the resources and requirements of men selecting active surveillance or engaging in long-term active surveillance. A recent qualitative study suggested six requirements of men on active surveillance (See Chapter IV - (110)): (1) general information on PC and how to interpret results; (2) specific information on AS investigations, follow-up, mortality risk; (3) complementary options regarding diet, lifestyle, exercise; (4) variety of resources; (5) social support and interaction and (6) verification of integrity of information. These requirements were reflected in our own FGs. Men who had opted out of active surveillance felt particularly strong about this.

4.2.3.1. The clinical team

The patient relationship with the clinical team is an important variable in adherence to healthcare, but it is difficult to assess the nature of this interaction and to measure its components. Poor communication is traditionally measured in terms of a patients' inability to

recall clinician instructions, with patients failing to recall between one-third and one-half of statements given to them (111). One FG participant suggested:

Participant 9 (69y)…."The doctor didn't even let me sit down, he greeted me at the door and said your PSA is fine, see you next year. I had questions; I wasn't encouraged to ask them"….."after leaving the clinic I couldn't even remember what my PSA level was, I had to call the nurse later that same day. 'I was told all I needed to know was that I didn't need to worry myself – that was it, end of conversation".

Initial selection of active surveillance is strongly associated with multi-disciplinary care (112). However, whilst multidisciplinary clinics are recognised as advantageous in optimizing active surveillance choice, our FG feedback suggests that variability in personnel managing active surveillance leads to specific concerns regarding consistency. This was demonstrated through commentaries from several participants (Appendix 3 Panel 2).

However, the combination of CNS and doctor has been found to benefit men with prostate cancer. Tarrant (113) and Ream (114) both found that men who had accessed a CNS reported a more positive experience of their cancer management. Our FGs confirmed that a combination of medical and nursing staff was optimal in giving information and supporting men on active surveillance (Appendix 3 Panel 1).

4.2.3.2. Detailed and consistent information

Information has a variety of benefits for cancer patients, particularly anxiety reduction, improved ability to cope with treatment and better self-care. Information can help empower patients. Recognition of the role that support and information plays in effective cancer care is not new. In 2002, NICE commissioned a report focusing on improving outcomes in urological cancers (115). It recognised that in prostate cancer in particular, the appropriate management strategy may depend on an individual's values and attitudes, but should include: Information about basic anatomy and pathology, prostate cancer and the individual variation in its impact and rate of progression, treatment options, probability of survival, symptom reduction, risks and potential short- and long-term effects. Our FGs demonstrated frustration in this respect, describing a lack of clarity that appeared to extend to the medical and nursing team (Appendix 3 Panel 4).

O'Callaghan (33), Oliffe (96) and Davison (31) found that patients on active surveillance became particularly stressed where information given by the clinical team was contradictory or inconsistent. Our FG participants also agreed that there was inconsistency, describing a lack of objective, robust information and poor descriptors of disease risk and active surveillance (Appendix 3 Panel 4).

The FGs discussed both delivery method and type of information and support required. All agreed with a 2010 FG study which reported that information on the internet was

contradictory, limited and difficult to find (116) and therefore a dedicated informational source was required.

Many of the men who had dropped out of active surveillance and had later chosen to undergo radical treatment also remarked on the inconsistent approach to information and support services between men offered active surveillance and those undergoing radical treatment.

Our group previously reported a significant increase in patient satisfaction when offered access to a peer-group educational seminar on radical prostatectomy (92). Galbraith *et al*. (117) described how this can provide a sense of meaning in men's experience of prostate cancer. Focus group participants also suggested that mimicking the information and support given to patients in other treatment groups may influence behaviour of the health professional team by endorsing active surveillance as a valid treatment option (95).

4.2.3.3. Diet and lifestyle advice

A 2015 systematic review of supportive care in prostate cancer highlighted self-care in nine papers (118). Authors discussed empowerment and sense of control that comes from self-care through lifestyle changes. Nanton found that 'In taking an active part in their own health management men were taking control of their illness'(119). This was also described by Oliffe

(96) and O'Shaughnessy (120) who demonstrated the merits of using strategies similar to men at other stages of disease combining 'living a normal life' with 'doing something extra', e.g. dietary or lifestyle changes. This appeared to increase both acceptability and adherence to AS and was also described by our FG participants (Appendix 3 Panel 5).

4.2.3.4. Study limitations

Our assignment of men to intervention and standard care was not randomised, but occurred over consecutive time periods as part of an audit/service improvement project where the intervention was the 'new' standard of care. It is not possible to exclude the influence of clinical practice that may have occurred over this time period e.g initial under sampling due to biopsy practitioner experience or learning curve of MRI imaging team. This may contribute in part to the higher proportion of men progressing in the intervention group, despite a significantly higher number of men in GGG1 at diagnosis.

Further, the two comparison groups differed in GGG, which may have influenced adherence. However, the differences remained statistically significant, even after adjustment for clinical characteristics such as GGG at diagnosis. We were, however, unable to adjust for other recognised confounding factors such as marital status, ethnicity and education level.

18 patients were excluded from the study as they failed to attend the seminar intervention. Follow-up with this patient group may have added value in reducing future non-attendances.

4.2.4. Conclusion

Findings from this study demonstrate that men on active surveillance desire consistency in contact with staff, appointments and information. Subsequent evaluation of this intervention demonstrates that a peer-group educational seminar, delivered by the clinical team in the initial months after starting active surveillance, reduces the likelihood of dropping out of active surveillance by 50%. With the trend towards active surveillance in LRPC increasing, interventions like this could help assuage the upward drift in healthcare costs worldwide.

4.3. Part 2: A systematic review of contemporary active surveillance practice.

This overview was published in Translation Andrology and Urology February 2018 (6) (Appendix 6).

4.4. Introduction

The increased use of active surveillance seen in some countries suggests that the global trend towards conservative management for LRPC is gathering pace, however the fact that there is no worldwide consensus on defining favourable risk disease (121) in active surveillance suggests that there is still some way to go in gaining universal acceptance.

This review aims to evaluate the literature describing contemporary active surveillance practices worldwide, identifying the differences in practice and exploring the importance of Movember's GAP3 (Global Action Plan Prostate Cancer - Active Surveillance) collaborative effort in answering the key questions: What defines safe patient selection? What should the surveillance strategy look like? What clinical triggers are important in recommending radical treatment?

4.5. Search strategy

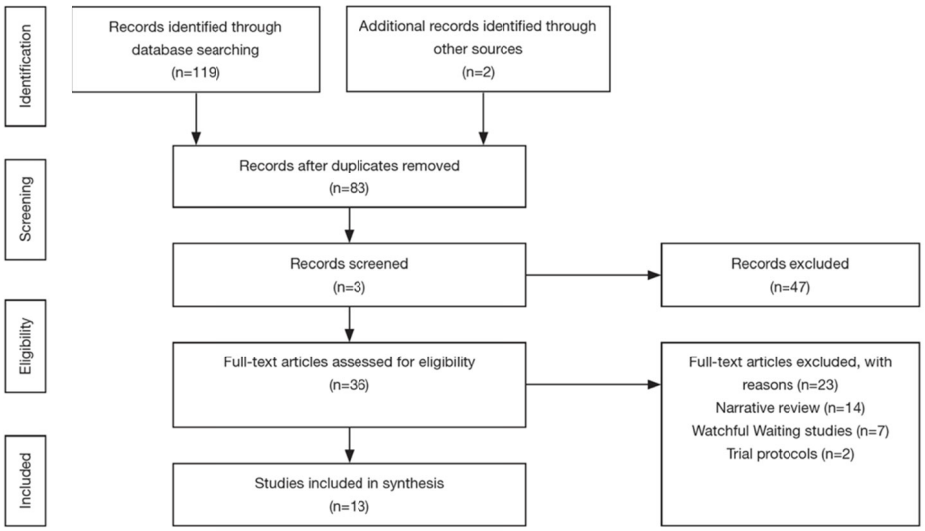
Studies documenting active surveillance cohorts with a minimum of five years' follow-up published before October 2017 were identified through a systematic search of electronic databases (PubMed/Medline 2000-now and Embase) using the following key search terms: "prostate cancer", "active surveillance", "follow-up", "cohort", and their relevant synonyms. Cited references were searched and retrieved for potentially eligible publications.

Studies of primary interest were those describing baseline and clinical characteristics of the study population, patient selection criteria, monitoring/surveillance protocol, AS drop-out, triggers for conversion to radical treatment and outcomes during follow-up (5-year studies with a median follow-up >18 months).

4.6. Findings

We identified 119 unique citations; of these 83 were excluded as review articles, commentaries, narratives, abstracts or where median follow-up was less than 18 months. Full-text screening was carried out on 36 articles, of which 23 were excluded, rendering 13 articles included (Figure 7) each describing a unique active surveillance cohort. Of the thirteen included cohort studies (107, 122-133), six took place in North America (122-124, 126, 128, 132),five in Europe (107, 127, 129, 131, 133), one worldwide (125) and one in Australia (130).

Figure 7 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram



The general demographic and follow-up characteristics of the published active surveillance cohorts in this review vary considerably (Table 6). The average age across the studies was 65 years-old. The number of participants studied ranged from 238 to 2,494 men. The number of months' follow-up ranged from 19 to 180 months.

The main findings in terms of active surveillance adoption/patient selection, monitoring protocols and trigger points for intervention or re-assessment across the different active surveillance studies are described below.

Table 6 Overview of large cohort active surveillance studies

Study	Study period	Country	Patient No.	Median Age (years)	Median PSA (ng/ml)	Follow up (median)	Prostate cancer specific survival (progression free survival)	Conversion to treatment	Conversion without evidence of clinical progression
MSKCC, 2011 (48)	Sept 1997 – Feb 2009	USA	238	64	4.1	1.8 years (in patients without clinical progression). 11% of patients were followed at least 5 years without progression	2 and 5-year progression-free probability 80% and 60% respectively	Not reported	Not reported
John Hopkins, 2015 (49)	Jan 1995 – June 2014	USA	1298	66	4.8	5 years (VLRPC), 3 years (LRPC)	99.9% (VLRPC), 99.4% (LRPC) at 10 years. 99.9% (VLRPC), 99.4% (LRPC) at 15 years.	50% at 10 years 57% at 15 years	17%
UCSF, 2015 (50)	1990-2013	USA	810	62	5.3	5 years	98% at 5 years (40%)	40% at 5 years	Not recorded
PRIAS, 2013 (51)	Dec 2006 – May 2012	Worldwide (17 countries)	2494	66	5.6	1.6 – 3.1 years	100% at 4 years.	34% at 4 years	9% (further 17.6% - solitary psa increase, urinary symptoms or patient preference)
University of Miami, 2010 (52)	Feb 1992 - 2009	USA	230	64	4.8	32 months	100% at 44 months	14% at 44 months	Not recorded
Royal Marsden, 2013 (53)	March 2002 – May 2011	UK	471	66	6.4	5.7 years	96% at 5 years	31% at 5 years	Not recorded
ProtecT, 2016 (54)	1999 – 2009	UK	545	62	Not recorded	10 years	99.4% at 5 years 98.8% at 10 years	54.8% at 15 years	38% at 15 years
University of Toronto, 2015 (55)	1995 – May 2013	Canada	993	68	Not recorded	6.4 years	98.1% at 10 years 94.3% at 15 years	25% at 5 years 45% at 15 and 20 years	1.6% (+/- 2% not reported)
University of Copenhagen, 2015 (56)	2002-2013	Denmark	317	65	6.6	5 years	Unknown	39.5% at 5 years	Not recorded
St Vincents, 2015 (57)	1998-2012	Australia	796	63	6.2	67 months	100% at 67 months	38% at 67 months	12%
Goteborg, 2016 (58)	Jan 1995-Dec 2014	Sweden	439	65	Not recorded	6 years	100% (VLRPC) at 10 and 15 years. 100% and 94%(LRPC) at 10 and 15 years. 98% and 90% (IRPC) at 10 and 15 years.	53% at 10 years 66% at 15 years	10% (further 8% urinary symptoms or unknown)
Canary PASS, 2016 (59)	2008 - 2013	USA	905	Not available	Not recorded	(8.4 months)	100% at 28 months	19% at 28 months	32%
Milan (SA-INT + PRIAS), 2017 (60)	2005-2007 (SA-INT) 2007 - 2016	Italy	818	66	5.7	59 months	100% at 59 months	50% at 5 years	32%

4.6.1. Active surveillance patient selection

Thirteen international active surveillance programmes met our inclusion criteria, describing guidelines for active surveillance patient selection (Table 7). These are described with respect to selection criteria based on the following components: (Tumour Nodes Metastases) TNM stage, PSA level, PSA density, percentage of cancer in prostate cores, number of positive cores and Gleason grading.

4.6.1.1. TNM stage

All cohorts agreed eligibility for active surveillance meant clinically localised prostate cancer, with half of the cohorts using T2a or less, two (John Hopkins (123) and Goteborg (131)) opting to follow the Epstein criteria of T1c (in at least one arm of their cohort study). At the other end of the spectrum, three studies also included patients with T2b (St Vincent's, Australia (130), Canary PASS (132) and Milan (133)) and two cohorts men diagnosed with T2c disease (Canary PASS (132)and Milan (133)) .

4.6.1.2. PSA level

Agreement between ten of thirteen cohorts suggested a PSA cut-off of 10µg/l, The University of Toronto (128) and Royal Marsden (127) suggested an upper limit of 15-20µg/l depending on life expectancy and age (>65 years) respectively. Only Goteborg (131) and Canary PASS (132) suggested an acceptable PSA for intermediate-risk disease of <20µg/l.

4.6.1.3. PSA Density

PSA density was featured in five cohorts (123, 125, 131-133). However, there was no consensus, with Milan (133) and PRIAS (125) suggesting a cut off of 0.2 and John Hopkins (123), Goteborg (131) and Canary PASS (132) opting for a more conservative 0.15.

4.6.1.4. Gleason grading

All included cohorts defined entry into active surveillance as men with low-risk disease - Gleason 3+3 or less. The Canary PASS (132) and Goteborg cohorts (131) defined an entry criteria for men with intermediate-risk disease as Gleason 3+4, whereas The Royal Marsden (127) suggested men over the age of 65 were acceptable for entry into active surveillance with Gleason 3+4.

4.6.1.5. Number of positive cancer cores

There was more agreement between institutions on the number of positive cancer cores (11 cohorts), which ranged between two and three cores in most cases. University of California San Francisco (UCSF) (124) suggested the number of cores should not exceed 33% of the total number of cores taken and the St. Vincent's Australia (130) cohort criteria suggested 20% as a reasonable cut-off.

4.6.1.6. Percentage of cancer in prostate core

Five of thirteen cohorts (Memorial Sloan Kettering Cancer Center (MSKCC) (122), Johns Hopkins (123), UCSF (124), Royal Marsden (127) and Milan (133)) agreed that no prostate core should contain more than 50% cancer with three cohorts (University of Miami (126), St

Vincent's Australia (130) and Canary PASS (132)) suggesting a more conservative 20-34% (126, 130). Five cohorts made no mention of percentage of prostate cancer in cores and therefore it is assumed this was not part of their selection criteria.

Table 7 Criteria for entry into active surveillance programme

	Criteria for entry into active surveillance programme								
Study	Maximum T Score / age / Life expectancy	PSA (µg/L)	PSA Density ng/ml (PSAD)	Gleason score	Minimum number of cores taken pre-AS selection	Maximum No. of positive biopsy cores (% of total cores)	Additional confirmatory re-biopsy	Maximum cancer length (percentage of biopsy core positive)	Imaging
MSKCC (122)	T2a	<10	None recorded	3+3	10	3	Yes	(50%)	No
John Hopkins (123)	T1c (VLRPC)	None recorded	<0.15	3+3	12	2	No	(50%)	No
	T2a (LRPC - Older men only).	<10	Not recorded	3+3	12	2	No	(50%)	No
UCSF (124)	T2	<10	Not recorded	3+3	Not recorded	(33% of total cores)	No	(50%)	TRUS
PRIAS (125)	T2	<10	<0.2	3+3	10	2	No	Not recorded	No
University of Miami (126)	T2	<10	Not recorded	3+3	10	2	No	(20%)	No
Royal Marsden (127)	T2	<15	Not recorded	3+3 or	Not recorded	(<50% of total cores)	No	(50%)	Not mandatory
	>65 years old	<15	Not recorded	3+4	Not recorded	(<50% of total cores)	No	(50%)	Not mandatory
ProtecT (107)	Aged 50-69 years. Clinically localised prostate cancer								
University of Toronto (128)	(1995-2013) T2a	<10	Not recorded	3+3	8	Not recorded	No	Not recorded	No
	(1995-1999) Patients aged >70 years	<15	Not recorded	3+4	8	Not recorded	No	Not recorded	No

	Criteria for entry into active surveillance programme								
Study	Maximum T Score / age / Life expectancy	PSA (µg/L)	PSA Density ng/ml (PSAD)	Gleason score	Minimum number of cores taken pre-AS selection	Maximum No. of positive biopsy cores (% of total cores)	Additional confirmatory re-biopsy	Maximum cancer length (percentage of biopsy core positive)	Imaging
	(2000-2013) LE <10 years + significant morbidities	10-20	Not recorded	3+4	8	Not recorded	No	Not recorded	No
University of Copenhagen (129)	T2a	<10	None recorded	3+3	6	3	No	Not recorded	No
St Vincents, Australia (130)	T2b (T2a (<55 years))	<10	None recorded	3+3	10	<20% of total cores	No	6mm (<30%)	No
Goteborg (131)	T1c (VLRPC)	Any	0.15	3+3	10 (6 up to 2009)	<3	No	(<50%)	No
	T1(LRPC)	<10	-	3+3	10 (6 up to 2009)	Not recorded	No	Not recorded	No
	T2(IRPC)	<20	-	3+4	10 (6 up to 2009)	Not recorded	No	Not recorded	No
Multi-institutional Canary PASS (132)	T1c (VLRPC)	-	<0.15	3+3	≥10 (within a year) or x2 biopsies - one within a year)	2	No	<50%	No
	T1c -T2a (LRPC),	<10 (LRPC),	-	3+3 (LRPC),	≥10 (within a year) or x2 biopsies - one within a year)	2	No	<50%	No
	T2b-T2c (IRPC)	10-20 (IRPC)	-	3+4 (IRPC)	≥10 (within a year) or x2 biopsies - one within a year)	2	No	<50%	No
	T2b-T2c (HRPC)	>20	-	3+4	≥10 (within a year) or x2 biopsies - one within a year)	2	No	<50%	No

	Criteria for entry into active surveillance programme								
Study	Maximum T Score / age / Life expectancy	PSA (µg/L)	PSA Density ng/ml (PSAD)	Gleason score	Minimum number of cores taken pre-AS selection	Maximum No. of positive biopsy cores (% of total cores)	Additional confirmatory re-biopsy	Maximum cancer length (percentage of biopsy core positive)	Imaging
Milan (SA-INT + PRIAS) (133)	T1c -T2a (+T1b if cancer <0.5cm3 + negative peripheral zone biopsies)	<10	-	3+3	2005 – 2012 – not recorded. Dec 2012- 2016 - Prostate volume dependant (PV <40cm^3 = 8; 40-60cm^3 =10, >60cm^3 = 12)	<20% of total cores (until Dec 2011) <25% of total cores (2011-2016)	No	<50%	No
	<T2c (PRIAS)	<10	<0.2	3+3 (3+4 if aged 70+)	Prostate volume dependant (PV <40cm^3 = 8; 40-60cm^3 =10, >60cm^3 = 12)	<2 or <15% of total cores if saturation biopsies taken (>20 cores) with a maximum of 4 cores positive	No	<10% core length in 3+4 disease only	Yes since 2015 – No limit on number of positive cores in patients with negative MRI or where targeted biopsy shows 3+3 disease only

LE = Life expectancy, VLRPC = Very low-risk prostate cancer, LRPC = Low-risk prostate cancer, IRPC = Intermediate-risk prostate cancer, HRPC = High-risk prostate cancer, SA-INT = Sorveglianza Attiva Instituto Nazionale Tumori)

4.6.2. Monitoring protocols

Following initiation of an active surveillance programme, most guidelines recommend serial serum PSA measurements, digital rectal examination (DRE) and surveillance biopsies to check for and identify indications of tumour progression (Table 8).

4.6.2.1. Digital rectal examination

Of the thirteen studies, DRE as part of the surveillance strategy played an important role in nine (MSKCC (122), John Hopkins (123) UCSF (124), University of Miami (126), Royal Marsden (127), University of Copenhagen (UCPH) (129), St Vincent's Australia (130), Goteborg (131) and Canary PASS (132)) with the frequency ranging from 3 to 6 monthly.

4.6.2.2. Prostate specific antigen (PSA)

All studies carried out PSA testing, but again protocols ranged from 3 to 6 monthly. Only MSKCC (122) recommended a 6-monthly free to total ratio PSA as useful.

4.6.2.3. Prostate re-biopsy

Eleven studies carried out confirmatory biopsies within a year of initial diagnosis, whilst the Royal Marsden (127) cited acceptability within two years of active surveillance initiation and ProtecT (107) required no repeat biopsy. All studies demonstrated differences in the frequency that biopsies were repeated thereafter. Two centres (John Hopkins (123) and University of Miami (124)) routinely biopsied annually, with the others ranging from 2-3 yearly or on clinical progression. Only the ProtecT study (107) did not perform routine and

regular re-biopsy. UCSF (124) was the only institution to carry out regular trans-rectal ultrasound without biopsies.

4.6.2.4. General health assessment

Regular routine general health assessments were undertaken in two studies (MSKCC (122) and Canary PASS (132)), as a possible criterion for switching to watchful waiting (WW), with only MSKCC indicating that they carried out regular lower urinary tract symptom assessment. Two centres (University of Toronto (128) and St Vincent's Australia (130)) indicated that they switched patients from active surveillance to WW at 80 years old and 75 years old, respectively.

Table 8 Surveillance strategy

	Surveillance strategy								
Study	**DRE (frequency in months)**	**PSA (frequency in months)**	**Free to total ratio PSA (frequency in months)**	**General health assessment**	**Urinary symptoms assessment**	**Imaging**	**Number of biopsy cores**	**1st re-biopsy scheduled (frequency in months)**	**Follow-up biopsy schedule**
MSKCC (122)	6/12	6/12	6/12	Yes	Yes	-	10 - 12	12-18/12	Every 2-3 years or change in DRE/sustained PSA rise
John Hopkins (123)	6/12	6/12	-	-	-	-	12	12/12	Annually
UCSF (124)	6/12	3/12	-	-	-	TRUS 6/12	12	9/12	Every 1-2 years
PRIAS (125)	-	3/12 (up to 2 years) then 6/12	-	-	-	-	Prostate volume dependant (PV <40cm^3 = 8; 40-60cm^3 =10, >60cm^3 = 12)	12/12	Year 4 & 7
University of Miami (126)	3-4/12 (2 years) then 6/12	3-4/12 (up to 2 years) then 6/12	-	-	Yes (ICI-SF)	-	Not recorded	12/12 (after 2000 – 10/12 cores taken at 9/12)	Annually (earlier if a dramatic rise in PSA or change in DRE)
Royal Marsden (127)	3/12 (year 1), 4/12 (year 2) then every 6/12	3/12 (year 1), 4/12 (year 2) then every 6/12	-	Yes	-	-	10-12	24/12	Every 2 years
ProtecT (107)	-	3/12 (up to 1 year) then 6-12/12	-	-	-	-	-	-	-
University of Toronto (128)	-	3/12 (up to 2 years) then 6/12	-	-	-	-	8 - 14	12/12	Every 3-4 years up to age 80
University of Copenhagen	3/12	3/12	-	-	-	-	10-12	12/12	Variable depending on patient risk (PSAD)

	Surveillance strategy								
Study	DRE (frequency in months)	PSA (frequency in months)	Free to total ratio PSA (frequency in months)	General health assessment	Urinary symptoms assessment	Imaging	Number of biopsy cores	1st re-biopsy scheduled (frequency in months)	Follow-up biopsy schedule
(129)									
St Vincents, Australia (130)	6/12 (3 years) then annually	3/12 (up to 3 years) then 6/12	-	-	-	-	-	12/12	At 1-2 years then every 3- 5 years. (Switched to watchful waiting once age >75 years/ life expectancy <7 years)
Goteborg (131)	3/12-6/12	3/12-6/12	-	-	-	-	-	No	Every 2-3 years or on clinical progression
Multi-institutional Canary PASS (132)	6/12	3/12	-	Yes	-	-	-	6/12 - 2/12	Year 2, 4, 6
Milan (SA-INT + PRIAS) (133)	6/12 (SAINT)	3/12	-	-	-	-	Since 2012, Prostate volume dependant (PV <40cm^3 = 8; 40-60cm^3 =10, >60cm^3 = 12)	12/12 then 24/12	Every 2 years
	6/12 (PRIAS)	3/12 (up to 2 years) then 6/12	-	-	-	-	Prostate volume dependant (PV <40cm^3 = 8; 40-60cm^3 =10, >60cm^3 = 12)	12/12	Year 4 & 7

PSAD = PSA Density, PSADT = PSA Doubling time, PSAV = PSA Velocity, TRUS = Trans-rectal ultrasound, MCL = Maximum cancer length, ICI-SF = International conference on incontinence short-form.

4.6.3. Triggers for intervention

At 5 years of follow-up, the proportion of men treated ranged from 14 to 50% across all of the studies. The proportion of men who developed metastatic disease was low across all studies, in the Johns Hopkins cohort (124) for example; this was recorded as 0.1 and 0.6% at 5 and 15 years, respectively. The prostate cancer-specific mortality rates were also low, ranging from 0.2% to 5.7% (122, 128) (Table 9).

Definitions of disease reclassification and progression differ across national guidelines and the active surveillance cohorts described here are different. Many of the cohorts describe changes in one or multiple criteria for initiation of definitive treatment (Table 9).

4.6.3.1. Pathology (Gleason score)

Amongst the thirteen cohorts reviewed here, eight studies (MSKCC (122), John Hopkins (123), UCSF (124), PRIAS (125), University of Miami (126), St Vincent's Australia (130), Canary PASS (132) and Milan (133)) triggered intervention in LRPC if subsequent pathology was Gleason score >6. In the Canary PASS LRPC group radical treatment versus continued active surveillance (with re-classification as intermediate-risk) were discussed as options. Two (University of Toronto (128) and Goteborg (131)) suggested any pathological upgrade would trigger intervention. Two cohorts (Royal Marsden (127) and UCPH (129)) identified a Gleason score of ≥4+3 as the trigger point. Only Canary PASS (132) and Goteborg (131) gave a weighting depending on very low-risk/low risk (Gleason >3+3) or intermediate/High-risk (Gleason ≥3+4) disease.

4.6.3.2. Number/percentage of positive cores

Five of the thirteen studies (MSKCC (122), UCSF (124), PRIAS (125), University of Miami (126) and Milan (133)) maintained that >2 cores positive should trigger treatment, with the UCPH (129) extending this to >3 cores positive. St Vincent's Australia (130) suggested that cancer found in >20% of any positive core should trigger intervention, whilst The Royal Marsden (127) and Johns Hopkins (123) suggested a higher threshold for triggering treatment: 50% and 33% respectively. The remaining studies gave no indication of cut-off based on number of cores positive. The maximum cancer length (MCL) was variable, with two centres (MSKCC (122) and John Hopkins (123)) suggesting a cut-off of 50% and two centres suggesting more conservative numbers; St Vincent's Australia (130) suggesting a cut-off of 8mm of cancer and the Canary PASS consortium was set at ≥34%. The University of Miami (126) defined any increase in volume of PC and in MCL as their trigger for intervention.

4.6.3.3. Prostate specific antigen

PSA-based triggers for intervention included PSA doubling time (PSAD) and PSA velocity (PSAV). Only two studies suggested PSA velocity as an important trigger, The Royal Marsden (127) suggesting a PSAV of >1 and St Vincent's Australia (130) >0.75. PSA doubling time was included in six studies (UCSF (124), PRIAS (125), University of Toronto (128), UCPH (129), St Vincent's Australia (130) and Milan (133)) with a cut-off of three years. The Goteborg group (131) defined the trigger as any PSA progression.

Table 9 Triggers for intervention (treatment or further characterisation)

	Trigger for intervention					
Study	**Gleason Score**	**Positive cores No. (%)**	**Maximum cancer length (MCL)**	**PSAV**	**PSADT (yr)**	**DRE**
MSKCC (122)	>6	>3	>50%			-
John Hopkins (123)	>6	(>33% of total cores)	>50%	-	-	-
UCSF (124)	>6	>2	-	-	<3	-
PRIAS (125)	>6	≥3		-	<3 (yearly repeat biopsies)	-
University of Miami (126)	>6	>2	Any increase in MCL	-	-	-
Royal Marsden (127)	≥4+3	(>50% of total cores)	-	>1ng/ml per year	-	-
ProtecT (107)	50% in PSA increase triggered review					
University of Toronto (128)	Pathology upgrade	-	-	-	<3 (MRI or repeat biopsy undertaken)	-
University of Copenhagen (129)	≥4+3	>3	-	-	<3	-
St Vincents, Australia (130)	>6	(>20%)	>8mm	>0.75	<3	T2b
Goteborg (131)	Any gleason or TNM upgrade	-	-	-	Any PSA progression	Any DRE change
Multi-institutional Canary PASS (132)	>6 (VLRPC, LRPC), >3+4 (IRPC, HRPC)	>2	(≥34%)	-	-	-
Milan (SA-INT + PRIAS) (133)	>6 (SAINT)	>20of cores (up to 2012), >25% cores (2012-2016)	>50%	-	<3	>T2c
	>6 (PRIAS)	>2	-	-	<3 (Where PSADT 3-10 years and biopsy not within 12 months – additional biopsy indicated)	>T2c

LRPC = Low-risk prostate cancer, IRPC = Intermediate-risk prostate cancer, MRI = Magnetic resonance imaging

4.6.4. Summary of systematic review

The thirteen active surveillance cohorts included in this review demonstrated a wide variety of descriptions of LRPC. This indicates a clear lack of consensus on defining favourable risk disease, suitability for active surveillance and intervention thresholds.

Patient selection (Table 7): Despite all studies agreeing that a clinically localised prostate cancer diagnosis was defined as T2 disease and the majority of studies agreeing on a PSA threshold of <10ug/l and Gleason score 3+3 (3+4 in intermediate risk disease), there was significant inconsistency in practice when considering pathology (i.e. the number of acceptable positive cores and maximum cancer length).

Monitoring protocols (Table 8): All studies agreed on PSA surveillance with a frequency ranging from 3 to 6 monthly and most agreed that a confirmatory biopsy was required within 12 months after AS selection; however, no consensus was reached on the importance and relevance of DRE or re-biopsy strategy.

Triggers for intervention (Table 9): The cohorts described here appear cautious in their definition of disease progression, with low tolerance for increasing PSA defined as “any” or number of positive cores, cancer volume, and/or change in Gleason score. There was no universal agreement on triggers for intervention although, agreement was reached on Gleason score >6 in 62% of studies, number of percentage increase in positive cancer cores

was identified in 69% of the cohorts, maximum cancer length and PSA doubling time of < 3 years was used in 46% of the studies.

A narrative review performed in 2016 showed that existing guidelines regarding active surveillance for prostate cancer vary widely, but predominantly state that the most suitable patients for AS are those with pre-treatment clinical stage T1c or T2 tumours, serum PSA levels <10ug/l, biopsy Gleason scores of ≤6, a maximum of two tumour positive biopsy core samples and/or a maximum cancer length of 50% per core sample (94). The heterogeneity in practice demonstrated in this narrative, further highlights the need for a robust collaborative worldwide prospective study to finally determine safe patient selection, monitoring and appropriate triggers for intervention.

4.7. The future of AS

4.7.1. Imaging

The use of Magnetic resonance imaging (MRI) in the context of active surveillance varies between practitioners, countries and healthcare systems. Current European (134) guidance on prostate magnetic resonance imaging (MRI) concentrates on its role in the detection and staging of PC. Little evidence has yet been published supporting more generalised use in the context of active surveillance.

This may explain why only two of the thirteen cohorts reviewed (the Milan arm of the PRIAS study (133) and University of Toronto) used MRI to support active surveillance at the time of reporting. The Milan group used MRI imaging routinely (from 2015) as an adjuvant to the

active surveillance selection criteria, opening up active surveillance selection to men with negative MRI scans. No limit was placed on number of positive cores in patients with negative MRI's or where targeted biopsy shows 3+3 disease only. The University of Toronto used MRI as a conduit to triggering intervention. Where patients had a PSADT of <3 years, MRI and/or repeat biopsy was used to clarify the need for treatment.

In 2015 a systematic review of MRI use in active surveillance found only seven studies addressing MRI reliability in relation to selecting patients for active surveillance using biopsy correlation and two studies focused on the use of repeat MRI in AS (135). This review was hampered by the small number of patients in the included studies as well as the low number of studies. It was concluded that MRI could detect clinically significant prostate cancer, however as of yet MRI cannot be considered as an alternative to repeat biopsy in long-term monitoring on active surveillance without further evidence from robust prospective studies.

Despite the paucity of evidence, in 2014 the UK NICE prostate cancer guidelines (Appendix 4 (26)) suggested a role for MRI in active surveillance, but without any guidance on the criteria for radiological significance and progression. With this in mind, the European School of Oncology recently reported the PRECISE recommendations (136) for MRI usage in active surveillance, with the aim of facilitating the development of a robust evidence base for documenting changes in prostate MRI findings in men on active surveillance over time. This checklist will allow for better assessment of the natural history of MRI change in men on active surveillance.

4.7.2. The role of nomograms in active surveillance

Nomograms have been successfully used and integrated into healthcare setting as an assist to both patients and clinicians in establishing risk and aiding decision making. There is widely accepted usage of nomograms in prostate cancer diagnosis (137, 138). However, predictive nomograms for indolent disease in the context of active surveillance have been less successful (139). In 2016 Verderbos and colleagues studied participants of the European Randomized study of Screening for PC (ERSPC) (140) to establish whether a probabilistic nomogram could improve patient selection for active surveillance compared to a rule based criteria. They reviewed men initially diagnosed with histopathological indolent prostate cancer at radical prostatectomy [defined as pT2, Gleason pattern </=3 and tumour volume (TV) </=0.5 ml or TV </= 1.3 ml] to develop an existing nomogram to provide probability-based data and compared this to rule-based selection according to the prostate cancer Research International: Active Surveillance (PRIAS) (125), University of Toronto (128), and Johns Hopkins (123) criteria. The performance of the nomogram, using the Johns Hopkins (123) and PRIAS (125) rule-based criterias, were found to be comparable and could prove a good alternative to rigid rule-based surveillance protocols, where patients request more information on probability of progression to make informed decisions on treatment.

4.7.3. Global Action Plan Prostate Cancer Active Surveillance (GAP3) initiative

Although active surveillance has evolved to a broadly accepted management strategy for men diagnosed with LRPC, this systematic review of worldwide active surveillance practices confirms there is little consensus on inclusion criteria, surveillance schedules and

intervention thresholds. Also, variation in active surveillance semantics used in literature and guidelines could lead to confusion.

To address these issues, the Movember Foundation launched within their Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) in August 2014 (141) . To date, GAP3 has united as many as 25 institutions, hospitals and research centres from the USA, Canada, Australia, Singapore, Japan, Korea, UK, Ireland, the Netherlands, France, Sweden, Finland, Switzerland, Italy and Spain. The primary aim of the GAP3 initiative is to create global consensus on the selection and monitoring of men with low risk PC, ultimately resulting in worldwide uniform guidelines.

Within the GAP3 initiative, the largest centralized prostate cancer AS database to date was constructed by combining patient data from 25 established AS cohorts worldwide. This database currently comprises clinical, marker-related and imaging data on more than 15,000 patients. Multiple data analysis of this unique global data set are currently on-going with focus on three main questions regarding AS: which patients are most suitable for AS, what is the most appropriate follow-up schedule and what is the right moment to switch to active treatment?.

Initial review of this database was published in 2019, and defined the reasons for opting out of active surveillance in the >10,000 patients registered. This showed that at 5 years, 12.8% (95% CI: 12.0–13.6%) of men converted to active treatment without evidence of disease

progression, however the proportion of men converting to active treatment without evidence of progression remained stable from around 7 years onwards (42).

In addition, the GAP3 programme is performing a centralized pathology review of randomly selected biopsies. Preliminary results confirm consistent biopsy quality and grading across the different centres, which would enable data analysis without correction. Moreover, a panel of leading prostate cancer specialists in the field of active surveillance was convened to overcome the active surveillance semantic heterogeneity in literature and guidelines (121). By using a modified Delphi consensus procedure including a three-round sequence of online questionnaires and a face-to-face consensus meeting, formal consensus was reached for all 61 individual terms.

Movember allocated additional funding in 2017, to maintain the database and update the clinical data annually with a special focus on MRI, quality of life and genomics data. MRI is becoming an increasingly important technology for the management of active surveillance. GAP3 aims to also assess the value of MRI with respect to lesion definition and changes over time.

In 2019, Prostate Cancer UK commissioned a consensus process to define statements on current best practice of active surveillance in the UK, informed by patients and clinical experts. Three sources of data were used: a systematic literature search of national and international guidelines; data arising from a Freedom of Information Act request to UK urology departments regarding their current practice of active surveillance; survey and

interview responses from men with localised prostate cancer regarding their experiences and views of AS. An Expert Reference Group then made some best practice patient-centred recommendations for active surveillance where consensus was achieved. These included; a personalised AS plan specifying PSA frequencies and thresholds for re-investigation, should be developed by the treating Urologist taking into account individual patient factors (i.e. age, comorbidities, etc) and their previous total PSA and PSA density. This plan should be shared with the patient and their GP to ensure all parties are clear on the individualised approach to AS for the patient. There is a strong emphasis on providing men who are offered active surveillance with specialist information and support through the decision-making process (142).

In summary, analysis of the global active surveillance data within GAP3 will elucidate the optimal inclusion criteria, surveillance schedules and intervention thresholds which should help inform more uniform active surveillance guidelines in the future.

This will enable clinicians to more confidently identify men who are suitable for active surveillance and to also decide whose prostate cancer has progressed and will, therefore, require treatment. In addition, this will reassure men in making the most informed treatment decision for their type of disease.

4.8. Conclusion

In the last 15 years large cohort studies have progressed the definition of safe active surveillance. Collaborations between institutions (ProtecT (UK) (107) and Canary PASS (US)

(132)) and even countries (The PRIAS study (125)) have contributed to our increasing confidence in active surveillance and a demonstrable increase in the number of men selecting active surveillance.

This systematic review shows that active surveillance is being applied. However, implementation of successful active surveillance programmes worldwide needs to reduce the over treatment of prostate cancer as well as creating a safety net for men incorrectly diagnosed with indolent disease. Currently, the general Urologist and/or Oncologist may struggle to manage these patients with any degree of confidence (which may explain variations in practice). This confidence requires robust data from large cohorts with long follow-up, such as collected within the GAP3 initiative, to create global consensus on inclusion criteria, surveillance schedules and intervention thresholds.

4.9. Part III: Systematic review of factors that influence active surveillance choice and adherence

Part III of Stage 1 aims to define the factors that influence active surveillance choice and adherence. The findings of this systematic review were published in European Urology Sept 2018 (95) (Appendix 7) and additionally highlighted as a National Institute of Health Research (NIHR) Signal (August 2018 (143)). NIHR Signals provide decision makers in the NHS, public health and social care with the latest important research from the NIHR and other health research organisations.

4.9.1. Introduction

Large active surveillance cohort studies (Table 6) reporting over the last five years have shown little physical morbidity and low prostate specific mortality whilst on active surveillance: 0.1% to 5.7% over 10 – 15 years (6, 144), observations which have recently contributed to an increased uptake of this management strategy (5, 145).

As already outlined, active surveillance uptake continues to vary across countries, practices and amongst physicians (7). This was most noticeable in the US CaPSURE database, which reported a sharp rise in the uptake of AS, from 10% over the past two decades to 40% in 2010-2013 (5) and the Swedish National Prostate Cancer Register which noted a rise from 40% to 74% between 2009 and 2014 (35). In Australia, where the healthcare culture is fairly evenly split between private and public systems, a 25% overall recruitment to active surveillance was recorded by the Victoria PC Registry during the period 2008-2012 (43).

However, in Sweden, where healthcare is delivered largely by the public sector, the proportion of men selecting AS was significantly higher (80-90% of eligible men) (35). Understanding the drivers for this variation in practice is essential.

In cohort studies reporting on active surveillance adherence, a large proportion of men continue to drop out of active surveillance, despite no evidence of disease progression (Table 6). Much research has focused on the influence of anxiety and depression on adherence. Cancer Research UK describes depression as an established response to a diagnosis of cancer, unrelated to stage or severity (41). However, in active surveillance the risk of moderate to severe depression (requiring treatment) has been reported as relatively low in comparison to other tumour groups, at 5% (146).

There is thus a need to first identify and understand the barriers and facilitators to active surveillance to provide the scientific basis for this proposed research project. The purpose of this paper was therefore to systematically evaluate the literature for factors affecting choice and adherence to active surveillance as a management strategy for LRPC.

4.9.2. Evidence acquisition

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (147).

4.9.2.1. Search strategy

Studies published between 2002 (when active surveillance was first described in the literature (148)) and December 2017 were identified through a systematic search of

electronic databases (PsychINFO, PubMed, Medline 2000-now, Embase, CINAHL and Cochrane Library (Table 10).

Table 10 Healthcare and medical databases used in literature search

Healthcare/medical database	Notes/rationale	Thesaurus
CINAHL (Cumulative Index of Nursing and Allied Health Literature)	Database for nurses and allied health professionals. Smaller than Medline but contains many unique records not found there.	Thesaurus known as CINAHL Subject Headings. Thesaurus known as Embase Subject Headings (many terms overlap with MESH).
Cochrane Library	Several databases of systematic reviews and clinical trials.	Uses MESH.
Embase (European medical database)	Overlaps with Medline between 40-60% with many unique records. Does not index nursing and allied health professional journals as a rule but will feature articles with wider relevance.	Thesaurus known as Embase Subject Headings (many terms overlap with MESH).
Medline (PubMed)	Largest medical database in the world containing records from 1951 onwards. Includes wide variety of disciplines including medicine, nursing, physiotherapy, occupational therapy, health management, psychology and psychiatry.	Thesaurus known as MESH (Medical Subject Headings).
PsychINFO	Psychiatric and psychological database containing literature from the 19th century onwards. Includes records from specialist journals as well as more general journals	Own thesaurus

This search strategy focused on the use of keyword search terms to identify studies based on active surveillance active surveillance? : Prostate cancer prostatic neoplasm, active surveillance OR watchful waiting, facilitators OR barriers, treatment adherence OR treatment compliance, treatment OR therapy OR therapeutics and decision making. The full search strategy is identified in Figure 8. References were also searched for eligible publications.

Figure 8 Search Strategy

Prostate Cancer:

("prostate cancer" "Prostatic Neoplasms"[Mesh]) ?

Active Surveillance:

("active surveillance"? OR "Active Surveillance" OR "watchful waiting" OR "Watchful Waiting [Mesh])

Barriers/Facilitators:

("facilitators*"[ti] OR "barriers*"[ti] OR "treatment adherence*"[ti] OR "treatment choice" "[ti] OR "treatment selection"*[ti] OR "treatment compliance*"[ti] OR ((treatment[ti] OR

4.9.2.2. Study eligibility and selection

Eligible studies for inclusion in the final analysis were those that evaluated choice and/or adherence to active surveillance rather than watchful waiting (WW). Although there are similarities between choice of active surveillance and WW, they are conceptually different management strategies (active surveillance is a strategy employed to monitor a patient where there is intention to offer radical treatment with curative intent when/if required, WW

implies no intention to offer curative treatment). Hence, studies where active surveillance and WW sub-groups were combined were excluded to reduce bias.

We considered studies eligible if they were original articles with a qualitative or quantitative design generating data on decision-making in LRPC when active surveillance was considered as a primary treatment option. Eleven studies were excluded on the basis of poor study quality or mixed WW/ active surveillance sub-group (149), as were qualitative studies that failed to state that saturation of information had been reached, usually ≥20 participants. Studies including at least 20 participants is a general guideline in qualitative research to reach data saturation (150). One study that fell beneath this threshold was included as information saturation was demonstrated.

Cohort/Registry studies were included when they were multi-institutional and included >500 patients to reduce the associated risk of bias in small sample sizes and increase the external validity and generalisability. Studies reporting on active surveillance adherence also included ≥2 years of follow-up. An overview of the included studies can be seen in Table 11.

4.9.2.3. Data quality

Qualitative and mixed methodology studies were evaluated for quality using The Purpose, Respondents, Explanation, Findings and Significance (PREFS) Quality Checklist (149). This checklist was previously developed by Bridges et al. for assessing quality of reports in systematic reviews of literature on patient preferences and comprises questions regarding

five aspects of each study: purpose (P), Respondents (R), Explanation (E), Findings (F), and Significance (S). The complete PREFS checklist is shown in Table 12. Appendix 8 outlines the quality questions. A quality score was calculated by adding one point for each "yes" answer on the PREFS checklist, with a maximum potential score of 5. Papers were categorized in a similar way to that reported by Joy et al (149): Standard Gamble (SG, i.e. HRQoL's) – 17 papers; contingent evaluation (CO, i.e. survey) – 14 papers; stated preference other (SPO, i.e. monetary value or choices or ratings) – 3 papers; qualitative (i.e. interviews) – 13 papers and 3 papers with mixed methodology.

The mean PREFS quality score was 3.46 (SD 0.54), and the scores ranged from 2 to 5. The mean quality scores were 3.15 (SD 0.55) in studies with qualitative methods, 3.33 (SD 0.57) in studies with SPO methods, 3.76 (SD 0.44), in studies with CO methods, 3.58 (SD 0.51), in studies with SG methods and 3 (SD 0), In studies with mixed methodology. 46 studies explicitly stated that the purpose (P domain) of the study was to evaluate factors affecting choice or adherence to AS, and 31 studies included all respondents in the evaluation of findings (F domain). There was more variability among the studies in satisfying the R, E, and S domains of the PREFS checklist, demonstrating that many reports lacked detail regarding whether responders were similar to non-responders and failed to include statistical tests to evaluate results where possible.

The included cohort/registry epidemiology papers were assessed for strength of evidence. Although no quality assessment tool completely fitted the purpose of this review,

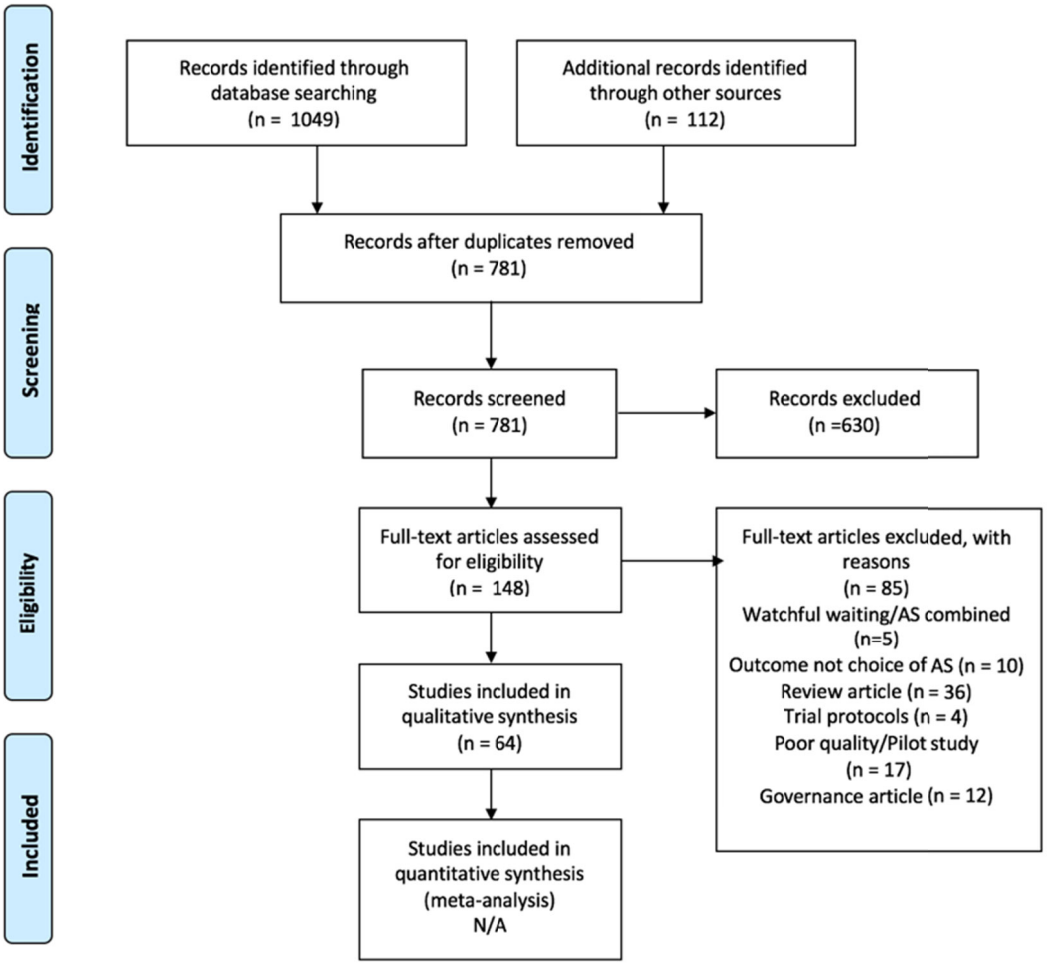
assessments were made using a modified Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) checklist (151) (Table 13). The following items were assessed: number of participants, variables (clear explanation of all outcomes, exposures, potential confounders and effect modifiers), data source (details given of measurement), bias (effort made to address potential sources of bias), statistical methodology (description of methods, missing data addressed, sensitivity analysis performed), descriptive data (characteristics of individuals given: demographic, clinical and social) and limitations (generalisability addressed, cautious interpretation). In each of the seven categories 1 point was assigned to each positive response, giving a possible total score of 12.

The mean quality score was 8.78 (SD 1.8). The scores ranged from 5 to 11. All studies included outcome variables, a full description of statistical methodology, clinical data and limitations. The highest level of variability was found in relation to bias, missing data and sensitivity analysis. Five papers scored ≥10.

4.9.3. Evidence synthesis and extraction

We identified 1,049 unique citations; of these 901 were excluded as review articles, commentaries or narratives. Full-text screening was carried out on 148 articles, of which 85 were excluded, rendering 64 articles included for synthesis (Figure 9). Given the heterogeneous study designs, no statistical comparisons were made.

Figure 9 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram



This mixed-methods systematic review uses a modified version of The Joanna Briggs Institute – Methodology for JBI Mixed Methods Systematic reviews (Integrated approach) (85). Joanna Briggs Institute integrated methodology combines both qualitative and quantitative data into a single mixed methods synthesis (85). A meta-aggregation of data is presented using a Bayesian approach, whereby all data was codified into themes and then presented in a meta-aggregation This approach generates summative statements of the evidence to equally inform the topic in a mutually compatible format (86), as seen in Table 14. The six themes identified were: cancer characteristics, patient, family and social support, provider, healthcare organization/practice and health policy.

Three authors (NK, MVH and SC) independently screened all titles and abstracts. The resulting reference list was compiled for full-text screening and data extraction. The final reference list was screened and agreed by all authors. A data abstraction form was developed for both qualitative and quantitative studies, based on review of the first articles of each type from among the selected papers. One author (NK) extracted data onto a spreadsheet, which was checked by two other authors (SC and MVH). Data abstraction was performed separately by two reviewers (NK and SC or MVH). Data extraction included: publication year, authors, journal name, title, study design, setting, population, eligibility criteria for participants, data collection method, response rate, and outcomes (Table 11). The review of findings/themes was open-ended with no pre-specified coding system, with intent to describe the primary conclusions of the authors.

4.9.4. Study design of included studies

Table 11 summarises the 64 included studies. 37 studies took place in North America, 20 in Europe, 5 in Australia, one compared America to Ireland and one was a worldwide study. The total number of study participants was 452,456, ranging from 7 to 189,768 in each study. The average age at diagnosis across the studies was 65 years.

The assessments were reported between 2007 and 2017. The studies consisted of 13 surveys, 12 qualitative interviews/focus groups, 12 cohort/registry studies, two content analysis and one intervention study and seven mixed method studies. 17 studies reported Health related quality of life (HRQoL) and/or psychological assessment data using validated questionnaires/tools (Appendix 9 - Panels 1, 2).

Some overlap in studies was noted with eight of 64 studies reporting on factors influencing both active surveillance choice and adherence.

4.9.5. Results – Barriers and facilitators to AS selection

This review has been split into two sections: Barriers and facilitators to AS selection and to AS adherence. These have been further synthesised and demonstrate influence on six different levels: cancer characteristics, patient factors, family and social support, provider, organisation and practice, and health policy. The sections below discuss facilitators and barriers according to these levels.

4.9.5.1. Cancer characteristics

4.9.5.1.1. Facilitators:

Nine studies described how cancer characteristics such as PSA, number of positive cores, Gleason score and tumour volume, influenced the selection of patients for active surveillance. A low Gleason score and a low PSA value were identified as facilitators of active surveillance in five of them (35, 112, 152-154). Five studies (36, 112, 152, 155, 156) also suggested that tumour volume played an influential role in active surveillance selection, with lower volume associated with higher levels of active surveillance selection.

4.9.5.1.2. Barriers:

The UK-based Prostate Testing for Cancer and Treatment (ProtecT) study, US based CEASAR Study and Swedish NCPR (National Prostate Cancer Register) (107, 108, 157) found that men with higher PSA's and tumour staging were disinclined to choose active surveillance when diagnosed.

4.9.5.2. Patient level

4.9.5.2.1. Facilitators:

Eight studies (31, 36, 156, 158-161) indicated that older men were more likely to choose active surveillance than younger men, but were in general less engaged in the decision-making process than younger men (31). Co-morbidity was featured in seven studies (35, 37, 112, 153, 158-160). The SEER registry reviews (37, 159), the US National Cancer Database (162), Swedish studies (35, 153), a US Multi-disciplinary clinic study (112) based in Boston and the Michigan MUSIC Study (152) showed an association between a higher Charlson co-morbidity index and choice of active surveillance. Orom et al. (158), however, found that the presence of cardiovascular disease was associated with a greater likelihood of choosing radiation over active surveillance. Both Orom's (163) and Parikh's (161) studies suggested that men with more years of education were more willing to opt for active surveillance, however another study suggested higher education was a barrier to active surveillance choice (153).

Six studies (28, 31, 32, 154, 164, 165) suggested that fear of side effects (in particular erectile dysfunction and incontinence) following radical treatment was a strong determinant of active surveillance. Ehdaie (166) found that significantly more men opted for active surveillance (12%), if during treatment counselling they had pro-actively been encouraged not to ignore potential harms of treatment.

4.9.5.2.2. Barriers:

Nine studies showed that younger men were less likely to choose active surveillance. Three studies (29, 31, 158) found men younger than 60 years old were less likely to choose active

surveillance. One comment from a patient in a qualitative interview was “choosing active surveillance would be irresponsible, ridiculous even - at my age (aged 53)”.

Other studies reported patient-related factors including ethnicity and family history of prostate cancer. Aizers et al (112) suggested that family history of prostate cancer increased the likelihood of an early drop out from active surveillance; this is consistent with Volks’ (28) interview findings that twice as many patients who opted for primary curative treatment had a relative with prostate cancer, compared to patients who opted for active surveillance. Xu’s study (155) showed that black men, as compared to white, were less likely to choose radical treatment, and specifically surgery, due to the high risk of adverse effects. In contrast, Oroms’ survey (158) suggested a racial difference in the use of active surveillance, with a higher proportion of black men choosing radiotherapy over active surveillance.

The association between the level of education and active surveillance is inconsistent: the Prostate Cancer Database Sweden (PCBaSe) (153) suggested that a higher level of education precipitates lower use of active surveillance in the low-risk prostate cancer group (26% of men versus, 39% with a mid-level education and 35% with a lower education level).

The psychological burden of active surveillance in respect of the associated repeat testing during active surveillance (33, 34), as well as the morbidity from repeat prostate biopsies (154), were also linked to reduced uptake of active surveillance. Wade (167, 168) found that men who were well informed about prostate biopsy were less likely to refuse repeat biopsy. This is important to acknowledge in the context of active surveillance where monitoring includes regular re-biopsy. However, several studies have described the process of repeat testing on active surveillance as a reassuring process (28, 33, 164).

4.9.5.3. Family and social support

4.9.5.3.1. Facilitators:

In all of the interview studies, men on active surveillance described justifying their decision to others as one of the most difficult aspects of the decision-making process. Both Xu and Goh (29, 98) reported that active surveillance referred to as “no treatment” was often more challenging for the spouse and children to understand than for the patient. Successful reassurance and education of the family was highlighted as a key facilitator to patients choosing and adhering to AS (28, 29, 33).

Four interview studies from the US, UK and Canada (28, 31, 33, 154), showed that “avoidance of treatment side effects”, “more convenient for lifestyle” and a “combination of reasons” were recurring themes explaining the choice of active surveillance. The UK study (154) also showed that men were equally as satisfied with their decision to undertake active surveillance as those who had undergone radical treatment two years later.

4.9.5.3.2. Barriers:

Pressure from family and friends has been found to be high at the point of diagnosis, many of whom urged curative treatment (29, 34). To give an example, in qualitative interviews performed by Xu et al (29) one man stated that he initially preferred active surveillance plus nutrition supplements to avoid treatment-related side effects, but that his family pressured him to choose radical prostatectomy and, as a compromise, he finally chose radiation. In another example, one man stated that he felt unspoken pressure from his family to choose curative treatment.

Perception and acceptance of active surveillance requires careful management. Orom's 2017 survey (158) described that high levels of distress at the time of diagnosis and at the time of the treatment decision were a predictor for choosing radical prostatectomy over AS. In contrast, Xu et al (155) found that black men were more likely to report higher levels of "cancer worry", but that their perception of the negative effects of radical treatment often led to fewer men choosing radical treatment.

4.9.5.4. Healthcare provider level

4.9.5.4.1. Facilitators:

Eleven of the reviewed studies suggested that the clinician heavily influences the decision-making process (30-34, 36, 98, 158, 166, 169, 170). Scherr, Liu and Davison all found that the diagnosing Urologist was the most influential clinician associated with AS choice (31, 36, 170). Orom's 2017 survey (169) found that a poor relationship between patient and clinician was mentioned by only 1% of men who were appropriately recommended active surveillance for LRPC, but by as many as 53% of men who were recommended a definitive treatment only.

Loeb et al (30) found that clinicians were concerned about the burden of intensive monitoring and that they might miss disease progression. However, both Orom (169) and Loeb (30) found that shared decision-making would address this.

Health literacy is defined as an "individual's capacity to access, understand, communicate, evaluate, utilize, and make decisions based on health information" (171). Therefore, provision and access to relevant information is a consistent theme in both increasing the uptake of and adherence to active surveillance. Mishra at al (34) described the views of patients and their families in internet conversations over a 10-year period; they found that

access to unbiased information was associated with more patients opting for active surveillance. Four other studies (28, 31, 33, 164) reported similar results. Goh et al (98) found that men who perceived they were receiving consistent information felt more in control of their decision-making and experienced a greater degree of satisfaction and certainty in choosing active surveillance. Three other studies concluded that access to educational resources, in addition to professional and peer support (supported self-management), optimised the treatment selection process and empowered men "to take control" of their diagnosis and of their choices thereafter (34, 116, 164). However, in contrast Taylor and colleagues (156) found that even when patients had access to information and support, men who chose active surveillance were less likely to access these resources than those men choosing radical treatment.

A US multidisciplinary clinic study (112) found that active surveillance selection was further facilitated through a multi-disciplinary provider approach, removing the bias of treatment recommendation which is often associated with clinicians that carry out a particular treatment. Patients receiving treatment-counselling from two or more specialist clinicians were twice as likely to opt for active surveillance than radical treatment (43% versus 22%). This was further confirmed and described during semi-structured interviews by Lyons et al (172).

Ehdaie (166) further found that a systematic approach for communicating the merits of active surveillance using appropriate framing techniques, increased the proportion of

patients selecting active surveillance (69% pre- intervention to 81% afterwards) equating to a 30% relative reduction in unnecessary curative treatment.

Several studies have also reported that by slowing down the treatment decision-making process providers might influence an increase in the proportion of men choosing active surveillance (33, 34, 172). Volk and colleagues (28) found significance in men viewing their cancer as “low-risk” as it offered an opportunity to postpone treatment allowing sufficient time for technological advances in treatment. When asked if men chose active surveillance as a holding mechanism only or as a long-term solution, patients fitted into two groups: those who concluded selection of active surveillance meant avoidance of side effects and those that felt active surveillance gave them time to make a treatment decision.

4.9.5.4.2. Barriers:

Conversely, the clinician’s influence has also been listed as a barrier for choice of active surveillance. Mishras review of the changing trends in internet conversations over a 10-year period suggested that patients were increasingly receptive to considering active surveillance, but many questioned if physicians could provide an unbiased treatment recommendation (34). This concern was also articulated in four of the interview studies (28, 29, 33, 98) where patients expressed concern about the possibility of clinician bias at the time of consultation, with many of them recalling that they were either not offered active surveillance as an option or the patients perception of active surveillance was “doing nothing”. Scherr and colleagues (170) reviewed patient-physician interactions over the period that treatment decisions were

made and found that physicians were heavily influenced by age and Gleason score, but not by the value that patients put on treatment outcomes e.g. sexual dysfunction.

Both Parikh and colleagues (161) used the US National Cancer Database (NCDB) to review 40,839 men with low-risk prostate cancer in relation to a number of variables. They found that the barriers to active surveillance included living a longer distance from the provider facility, and those men diagnosed by a physician working outside of an academic or research facility.

4.9.5.5. Healthcare organisation and practice level

4.9.5.5.1. Facilitators and Barriers:

Many narrative reviews of active surveillance highlight differences in active surveillance protocols among healthcare providers, health care systems and also within individual countries (35, 36, 43, 152). For example, the MUSIC group found that the use of active surveillance varied substantially between different urology practices in the state of Michigan, ranging from 27-80% of eligible patients (36, 152). This variability could simply be attributed to the recommendation of the clinician, but two studies (28, 34) focused on access to clinical expertise and technology, suggesting that patients felt that they were only offered AS where there was availability of imaging facilities and expert clinicians to deliver the active surveillance protocol. A similar diagnostic practice related influence was also observed in the Michigan MUSIC study (36, 152).

Type of healthcare system as a barrier to active surveillance was mentioned in one study (30) which found that the US system placed limitations on a clinician's ability to recommend active surveillance (although did not find that this was due to financial incentives) and carry out the necessary regular re-testing associated with active surveillance. However, Parikh and colleagues (161) found that analysis of the NCDB suggested higher uptake of active surveillance in the uninsured.

4.9.5.6. Health policy level

4.9.5.6.1. Facilitators and barriers:

In 2006-2007, Mishra et al (34) reported that, patient and clinician attitudes towards active surveillance (calculated numerically as a "sentiment-index" in the content in internet conversations) were at their lowest, with both judging active surveillance "not safe" and "should only be offered to older patients". By 2009, Mishra et al found the internet sentiment-index was high, meaning there was a more positive attitude towards active surveillance. Reasons for this included a 2009 American Urology Association endorsement for AS (173) and a 2010 publication of a large scale active surveillance cohort (174) reporting a very low mortality rate over intermediate follow-up. In Sweden, Loeb and colleagues (35) also found that active surveillance uptake (2009-2014) significantly increased and hypothesised that this was largely due to National Guidelines recommending active surveillance.

4.9.6. Results – Barriers and facilitators to AS selection

4.9.6.1. Cancer characteristics

4.9.6.1.1. Facilitators:

Several population-based studies reported on cancer characteristics in relation to active surveillance adherence. The UK-based Prostate Testing for Cancer and Treatment (ProtecT) study, US based CEASAR Study and Swedish NCPR (National Prostate Cancer Register) (107, 108, 157) found that men with lower PSA's and tumour staging were more inclined to adhere to active surveillance.

4.9.6.1.2. Barriers:

The Swedish NPCR study (108) reported that the <65-year age group and those with higher education levels (<9 years full-time education) were significantly less likely to continue active surveillance than the older and less educated groups. These findings have been replicated in qualitative studies such as those carried out by Lang and O'Callaghan (33, 157), which found that younger men with higher educational level found the notion of long-term active surveillance, i.e. "doing nothing", less tolerable than the associated morbidity of radical treatment. The Swedish National Prostate Cancer Registry (NPCR) study (108) also reported that out of those men who discontinued active surveillance, 52% did so because of PSA progression and 24% due to biopsy progression.

4.9.6.2. Patient level

4.9.6.2.1. Facilitators:

Patient perceived experience of active surveillance featured in 3 studies. Goh (98) analysed the experience of active surveillance in 34 men and found that those who viewed their experience with cancer as having a positive impact on their lives were better able to manage the uncertainty of AS active surveillance and felt more in control of their decision-making, and during active surveillance. Oliffe (96) found that men reporting a higher level of positivity in the face of their cancer diagnosis (attributed to consistency in information and support) were less likely to exhibit decision-making conflict related to the perceived effectiveness of their treatment plan and therefore may be more inclined to remain on active surveillance. These studies suggest that careful patient selection is important for both treatment choice and adherence (96, 98). Volk et al (28) found that men described the process of active surveillance as an organized, supportive process of regular monitoring.

Four of the seven Health Related Quality of Life (HRQoL) studies had no control group (175-178). Wilcox and Jeldres (177, 179) found no change in HRQoL before or after entry into an active surveillance programme. Parker (178) found that as age and body mass index increased, HRQoL decreased over time. Both Parker and Bellardita (175, 178) found that >5 months after diagnosis and commencement of AS, HRQoL improved.

Bellardita (175) also noted that men with a partner and men who had >18 biopsy cores taken at diagnosis were more likely to have a good HRQoL on active surveillance. Hegarty (176) compared HRQoL between men on active surveillance in Ireland and the US: general HRQoL

and vitality was lower in the US group – which they reported was likely due to differences in health-care expectations.

The six studies that included control subjects of either men with no cancer (180) or those undergoing radical treatment (181-184) or both (185), showed no statistical differences in HRQoL between the control subjects and men on active surveillance. The Finnish section of the PC Research International: Active Surveillance (PRIAS) study (180) found better than average HRQoL (as defined by the RAND-36 Questionnaire – Appendix 9) than in the general Finnish male population, both immediately following entry into active surveillance and 1 year later.

Vanagas (181) and Venderbos (182) both reported better HRQoL in men on active surveillance than in men who had undergone radical treatment with respect to physical, emotional and social scales. Donovan and colleagues reviewed patient-reported outcomes comparing monitoring to surgery and radiotherapy as part of the ProtecT trial (183). The monitoring cohort consistently did better in respect to three of the four domains; erectile, urinary and bowel function, however there was no significant difference in HRQoL amongst the three treatment groups. Smith (185) found similar HRQoL scores across active surveillance and treatment groups. Chen and colleagues (184) reported similar results recently from the North Carolina Prostate Cancer Comparative Effectiveness and Survivorship Study (NC ProCESS) where contemporary prostate cancer treatments were compared to active surveillance in respect to HRQoL. However, after 24 months it was notable that QoL scores were not clinically meaningfully different between the treatment and active surveillance groups.

When measuring the anxiety associated with long-term surveillance adherence, the majority of studies included in this review suggested that anxiety reduced (180, 181) or remained the same over time (146, 175, 177, 186-189), with no observed impact on long-term adherence.

In the recently published ProtecT study, depression was reported in only 6% of the 545 men allocated to active monitoring over a period of 10 years, suggesting that depression and anxiety do not increase significantly whilst on active surveillance (107, 190).

A number of studies have shown that emotional distress is relatively high in men at the time of their prostate cancer diagnosis (158, 191). However, anxiety in men on long-term AS has been generally reported as favourably low. A 2015 systematic review (192) reported no overall difference between levels of anxiety following diagnosis of LRPC and during active surveillance, which was reported as between 4-15%. In fact, more studies have suggested that anxiety in men on AS reduces (180, 181, 186) or remains the same over time (146, 175, 177, 186-189).

4.9.6.2.2. Barriers:

The Swedish National Prostate Cancer Registry study (NPCR) (108) reported that out of those men who discontinued active surveillance, 20% stopped due to patient preference alone. The US based CEASAR Study (157), which included men from five Surveillance, Epidemiology and End Results (SEER) catchment areas, and the Cancer of the Prostate Strategic Urologic Research Endevour (CaPSURE) database (157) found that 8-23% of men converted to curative treatment for reasons of personal preference rather than disease progression.

These findings were further explored in two large qualitative studies exploring men's survival expectations as a result of selecting treatment for low risk PC. Xu (193) reviewed men's perceptions of the likely benefits and harms of radical treatment versus no treatment (active surveillance). This was calculated in the form of patient perceived life expectancy (LE). At the time of the survey, two thirds of the 229 men had started or completed treatment. Of these, 30% in the AS group expected to live <5 years. This was in contrast to in the treatment group where >95% of patients estimated their LE to be >5 years. Kendel (194) also reviewed perceptions of the risk of death from PC between matched patients who had undergone active surveillance or radical prostatectomy. Men who had undergone radical prostatectomy estimated the risk of dying from prostate cancer associated with active surveillance to an average of 51%, at least a 10-fold overestimation of the true risk. They believed that their 10-year risk of dying from prostate cancer after a radical prostatectomy was only one third of the risk of active surveillance (18% - also a substantial overestimation). Both studies thus suggest that patients' perception of survival is a barrier to both active surveillance selection and long-term adherence.

Although some studies suggested that "fear of cancer progression" may be a limiting factor to choosing AS (96, 195-197), none have convincingly shown that this contributes to a significant number of men opting out of active surveillance without documented clinical progression (Venderbos (197) found this was 5%). Both Davison (188) and Parker (178) found that the degree of "fear of progression" did not change significantly over a period of active surveillance.

4.9.6.3. Family and social support

4.9.6.3.1. Facilitators:

Four studies highlighted that successful reassurance and education of the family was a key facilitator to patients both in choosing and adhering to active surveillance (28, 29, 33). Loeb's (110) qualitative focus group and interview study found that social support and interaction (support groups, online forums, support for spouse and family) was of particular importance in active surveillance adherence. An active surveillance support group for both family and men with prostate cancer was a particularly strong recommendation. Mader (164) interviewed 15 men following their decision for active surveillance and found strong correlation between active surveillance adherence and social support, including spouse, extended family and experiences of others. Anandadas and colleagues (38) further demonstrated that men were equally as satisfied with their decision to undertake active surveillance as those who had undergone radical treatment two years later.

4.9.6.3.2. Barriers:

Pressure from family and friends is reportedly high at the point of diagnosis, many of whom urge curative treatment (29, 34). The experiences of friends and family members with cancer (often not prostate cancer) are consistently reported as a significant pressure in men on active surveillance (29, 34). Berger (198) noted men reported leaving active surveillance and pursuing treatment to limit their loved ones' worry, or in reaction to the fear of cancer expressed by their family. Partner anxiety was also documented by Seiler (199), who compared levels of anxiety and depression between men on active surveillance and their partner. Anxiety scores were much lower in the men than in their partners. The CaPSURE

database (157) found that 16% of men converted to curative treatment on the basis of "spousal encouragement".

4.9.6.4. Healthcare provider

4.9.6.4.1. Facilitators:

Seven studies identified facilitators to active surveillance adherence including; education, self-management techniques, healthcare professional and peer support in the furtherance of increasing active surveillance adherence. Loebs (110) combination of focus groups and semi-structured interviews found six themes relating to the facilitation of active surveillance adherence. Five of these were consistent with healthcare provider responsibilities in the form of informational needs; (1) information on prostate cancer (biopsy features, prognosis), (2) information on active surveillance (testing protocol, difference between active surveillance and WW), (3) information on complimentary options (diet, lifestyle), (4) variety of resources (source, format), (5) integrity of information (trusted source, secure, multidisciplinary). Oliffe (96) found that self-management strategies helped men cope with some of the long-term uncertainty of active surveillance, whilst 'The Prostate Cancer Lifestyle Trial' based on lifestyle modifications, including exercise and attention to stress management, demonstrated an improved treatment-free survival for men on active surveillance (97). Goh (98) found that men who perceived that they were receiving useful, consistent information were more satisfied with AS and therefore more likely to continue on active surveillance. Kinsella and colleagues (200) found that active surveillance classes significantly improved long-term adherence to active surveillance, as did consistency of personnel to support and inform patients as found in the UK based ProtecT Trial (99). Interventions relating to peer support

have also demonstrated a significant improvement in the quality of life of men with any stage of PC (99, 200).

4.9.6.4.2. Barriers:

The ability of healthcare providers to deliver long-term support to patients on active surveillance was highlighted in several studies (198, 201, 202). Men leaving AS describe a number of un-met supportive care needs (198). These include lack of education and clarity concerning the correct time to pursue treatment, and triggers for treatment both from a patient and relative perspective.

Two studies (201, 202) specifically focused on the influence of support groups. These noted either no effect or even a negative effect on long-term active surveillance adherence, possibly due to the group consisting of a mix of survivors, i.e. those who had undergone radical treatment and those on AS (202). Chapple (201) found support groups were of no help to men on active surveillance, with one man reporting that he felt he "had to defend himself "in the support group for choosing active surveillance.

Mishra (34) concluded that there was a lack of consistent and reliable information available to men during long-term active surveillance.

4.9.6.5. Healthcare organisation and practice level

4.9.6.5.1. Facilitators and Barriers:

Differences in surveillance strategies have also demonstrated an association with adherence both in a positive and negative respect (Table 14). These contemporary cohort studies all include a strategy of repeat biopsy as part of a robust active surveillance protocol. Two studies found that prostate biopsy was associated with significant morbidity and active surveillance adherence could therefore be influenced by frequency/requirement to re-biopsy. The ProBE (The effects of Prostate Biopsy) study nested within ProtecT, assessed patient response to prostate biopsy and indicated that 25% of men who had undergone prostate biopsy were dis-inclined to undergo subsequent biopsies (167), whilst a study by Bokhorst (203) as part of the PRIAS study suggested that complications following prostate biopsy were not uncommon (20% of men), and after complication men were less likely to accept repeat biopsy.

However, in two interview-based studies that took place in the US (28, 33), men gave a consistent description of active surveillance, viewing it as a reassuring, organised and supportive process despite invasive testing.

4.9.6.6. Health policy level

4.9.6.6.1. Facilitators and Barriers:

AS protocols in respect of patient selection, safe monitoring and triggers for intervention vary between study cohorts, healthcare systems and countries, which makes it difficult to produce a coherent, consistent clinical guidance document. In Sweden, Loeb and colleagues

(35) found that active surveillance uptake and adherence (2009-2014) significantly increased and hypothesised that this was largely due to clear National Guidelines recommending active surveillance. Likewise the PRIAS study (204) suggested improved compliance and adherence as part of an official active surveillance programme.

4.9.7. Results synthesis

The barriers and facilitators to active surveillance choice and adherence were categorised into six levels as part of this review: cancer characteristics, patient, family and tumour characteristics, patient factors, family and social support, provider, organisation and practice, and health policy. which are summarised in Table 14. These barriers and facilitators varied in both strength of association and level of evidence, and are described in Figure 10. The barriers and facilitators identified as most influential over the six levels are symbolised as circles, with larger circles representing a greater degree of evidence as supported by this review.

Figure 10 Barriers and facilitators to AS choice and adherence

Yellow circles = the evidence is strongest for active surveillance choice.
Green circles = the evidence is strongest for active surveillance adherence.
Brown circles = the evidence is relevant to both active surveillance choice and adherence.

4.9.8. Discussion

A demonstrable rise in the use of active surveillance has been noted over a short timeframe, however there are significant differences between individual healthcare providers as seen in the US CaPSURE Database (5) and Swedish PCBaSe (35). Local guidelines, national policy, patient education, supportive care, and medicolegal factors may be important factors driving this variation [10, 12] and therefore these issues require greater consideration and management if we are to better facilitate active surveillance.

Studies focusing on men's perception of risk as a barrier to choosing active surveillance show that men continue to grossly overestimate the risk of dying from LRPC whilst on AS (29, 31,

34, 154). Moreover, understanding the implications of HRQoL and psychological factors on the decision to both choose and adhere to active surveillance requires further multi-dimensional assessment and interpretation. Clinicians and patient groups actively encourage the increasing responsibility that prostate cancer patients are taking for self-directed management and informed decision-making (97, 205). Such patient empowerment has positive psychological effects on cancer patients in general and should be explored in the specific context of active surveillance (97, 205).

These elements have been explored in the context of the chronic disease setting, which one could argue relates well to a diagnosis of LRPC that may never require curative treatment. A systematic review of general health screening and treatment decision making in the chronic disease setting (206) found that clinicians employing a process of 'motivational interviewing' consistently improved patients knowledge, perception of risk, and increased confidence in decision making. Motivational interviewing is specifically designed to help patients identify and resolve ambivalence about changing their behaviour by exploring personal perspectives and perceived barriers (207). It employs a four-step guiding style (engaging, focusing, evoking, and planning) to foster a constructive clinician-patient relationship. Joosten (208) found that motivational interviewing improved the patients' ability to self-manage and increased adherence to chronic-disease management plans.

Although there is currently no published experience of motivational interviewing in active surveillance, a recent systematic review in other cancer patients (209) found that it was

useful for eliciting lifestyle behavioural changes, decreasing cancer related anxiety and encouraging supported self-management. This also supports the argument that men on active surveillance experience a similar physical and psychological burden to people living with other chronic conditions (210), such as asthma and diabetes (211-215), for whom quality of life relies on adherence to a treatment plan with the aim to optimize disease control, maintain quality of life, thus preventing unnecessary escalation of treatment.

Another systematic review (211) outlining the merits of supportive self-management in chronic disease adherence suggested that there are core components of support and that their implementation requires a holistic approach, which intervenes at the level of the patient, the health care professional and the organisation, much in the same way as identified in this review of active surveillance:

1) Provision of education about the long-term condition (LTC)

2) Psychological strategies to support adjustment to the LTC

3) Practical support tailored to the LTC (e.g. support around activities of daily living for disabling conditions and action plans in conditions subject to marked exacerbations)

4) Social support

5) Lifestyle modifications (e.g. diet and exercise)

Our current systematic review highlights the need for improved validated methods for patient and physician education to facilitate the uptake of active surveillance among men

with LRPC. Moreover, studies suggesting that clinician's bias may influence the treatment decision-making process (31-34, 36, 98, 158, 169) suggest that educational efforts aimed at clinicians and frameworks for how they deliver the information on treatment options (166) are important for increasing the acceptance of active surveillance. Education, appropriate information and support aimed at both the patient and their family have long been recognised as important in the management of chronic conditions (77, 78), with studies demonstrating an increase in adherence to treatment plans where these have been established.

In addition, many chronic disease studies have successfully explored strategies to reduce healthcare inequalities in chronic health conditions (214, 216, 217). This has been achieved through the standardisation of education and training to both clinicians and patients, development of educational materials and decision aids, as well as creation of specialist centres for chronic conditions. To date, one study has replicated this in the context of active surveillance. Formica and colleagues (218) reported that decision aids in combination with standardised patient education packages achieved a three-fold increase in active surveillance acceptance.

Several active surveillance papers suggested that National guidelines could have a significant impact on selection and adherence to active surveillance (34, 35, 204). This has been replicated in the chronic disease setting (215, 219). In diabetes management, the introduction of the Dutch Guidelines increased clinician adherence by 60%, suggesting that

guidelines are reassuring for both patients and clinicians (219). The current discordance in active surveillance management makes internationally ratified guidelines a priority, and efforts such as those employed by the GAP3 consortium (Movember) (94), which has established active communication and collaboration among research groups worldwide, are likely to change this. GAP3 aims to reach international consensus on the definitions and terms used in AS through analysis of a global database including >14,000 patients (94).

The requirement for continuous monitoring in active surveillance has been described as both a barrier and facilitator. In chronic disease management, it gave rise to early developments in telehealth with some studies suggesting that easy-to-learn applications can improve adherence, lessen disease impact, accelerate behaviour change to improve outcomes and increase patient and partner confidence during remote monitoring (220, 221). Active surveillance monitoring protocols are currently undergoing rationalisation, with more frequent imaging and less biopsies. Although we found no reports of the use of mobile health applications in the active surveillance setting and only one small pilot of an internet based application specifically aimed at managing uncertainty in active surveillance (222), the change in the way we survey patients could lend itself to the introduction of robust remote monitoring using this technology.

The role of social media in choice and adherence to active surveillance has not yet been explored;, however, on-line social networks have changed the way we communicate and provide new ways to engage patients. Twitter and Facebook groups established to engage

cancer patients offer easy access to peer support and have been associated with less stress, anxiety and depression (86-87) and in the chronic disease setting, Kirwan (223) found that combining (224) on-line applications and social networking significantly increased diabetic glycaemic control in comparison to the control group.

A combination of these core elements is critical to ensuring positive experience and benefit of living with LRPC on active surveillance. Advances in prostate cancer management including the use of multi-parametric MRI, and more sophisticated prostate biopsy strategies in both diagnostics and surveillance programmes could also change the level of reassurance in active surveillance. Alongside this, a recent systematic review focused on the development of genomic profiling suggests that combining genome-wide association studies (GWAS) data with gene expression and structural rearrangements and risk alleles could provide a new basis for developing a prognostication tool to guide therapy for men with LRPC (224).

4.9.9. Limitations

This review is limited as a mixed methodology paper. The included studies were heterogeneous and therefore a meta-analysis was not possible. This type of systematic review relies on a reasonable number of included studies for strength, however the weighting of individual studies needs to be adjusted based on the varying levels of evidence and methodological quality of the included studies. However, this has been represented using the PREFs quality checklist and a modified STROBE checklist, which was reviewed by the three reviewers independently.

Of the papers reviewed, some did not distinguish entirely between active surveillance and WW and therefore older age and co-morbidity as facilitators to active surveillance may be inaccurate in 2018. Another limitation concerns the generalisability. More than 50% of studies were North American, and this healthcare system may not be generalisable to other countries.

4.9.10. Conclusion

Many factors influence men's choice and adherence to active surveillance, such as the clinician's attitudes, family and social support and patient education. The clear recommendations of this review include agreed international guidelines on active surveillance and the introduction of a multidisciplinary management strategy with psychological support to facilitate the active surveillance. Current clinical practice at centres with high active surveillance uptake provide insight of the changes required to ultimately decrease the overtreatment of prostate cancer worldwide, whilst experience gathered in the chronic disease setting such as the introduction of supportive self-management, social media interventions and motivational interviewing, could form the blueprint for future active surveillance programmes to increase both choice of and adherence to active surveillance in LRPC. However, it is clear that patient and public involvement is required to further refine the priorities of men on active surveillance and to provide consensus on supportive care strategies for active surveillance adherence.

Table 11 Overview of the studies

included in the systematic review on factors affecting choice and adherence to active surveillance in men with low-risk prostate cancer.

#	Author	Year	Reference	Design	N or Response rate (%)	Country	Study population/ setting	Data collection method (instrument)	Study period	Age (mean)
1	Davison, et al	2012	(31)	Cross-sectional **survey** to AS patients	180/258 (70%)	Canada	Clinical/ Hospital	Survey (Likert scale)	2009-2011	67
2	Goh, et al	2012	(98)	Cross-sectional **survey** to AS patients	34/34 (100%)	USA	Research/Support Group	Survey/Interviews	May-August 2011	63
3	Orom, et al	2014	(169)	Cross-sectional **survey** to AS patients	120/126 (79%)	USA	Clinical/Hospital	Survey	2010-2012	65
4	Xu, et al	2016	(155)	Cross-sectional **survey** to patients with localized PC	260/559 (68%)	USA	Population Database	Survey	2009-2010	61
5	Orom, et al	2017	(158)	Prospective **survey** of patients undergoing AS/RP/RT	1,531/3,337 (46%)	USA	Database/ Hospital	Survey (Distress thermometer - 11 point analogue scale)	2010-2014	Unknown
6	Anandadas, et al	2011	(154)	Prospective **survey** to AS patients	768/768 (100%)	UK	Clinical/Hospital	Survey (RAND-36 Item – SF-36 v.2, UCLA-PCI, study-specific survey)	2000-2006	65
7	Gorin, et al	2011	(32)	Prospective **survey** to AS patients	105/185 (57%)	USA	Clinical/ Hospital	Survey	Unknown	66
8	Loeb, et al	2016	(30)	Qualitative **interviews** with PC clinicians	24	USA	Hospital/ Community	Interviews (thematically analysed)	2015	N/A
9	Volk, et al	2014	(28)	Qualitative **interviews** with AS patients	30/36 (83%)	USA	Clinical/	Interviews	2011	63

				and RP/RT patients			Hospital	(thematically analysed)		
10	Xu, et al	2012	(29)	Qualitative **interviews** with patients with LRPC	21	USA	Research/ Clinical community	Interviews (thematically analysed)	Unknown	58
11	O'Callaghan, et al	2014	(33)	Qualitative **interviews** with patients with LRPCand their partners	21 men and 14 partners	Australia	Clinical/ Hospital and community	Interviews (thematically analysed and inter-rated)	2012-2013	Range 61-70
12	Aizer, et al	2012	(112)	Retrospective **cohort/registry** study	701	USA	Clinical/ Hospital	Database	Unknown	62
13	Loeb, et al	2013	(153)	Retrospective **cohort/registry** study	57,713	Sweden	Population database.	Database	1998-2011	65
14	Filson, et al	2014	(37)	Retrospective **cohort/registry** study	7,347	USA	Population database	Database	2004-2007	66+
15	Hoffman, et al	2014	(159)	Retrospective **cohort/registry** study	12,068	USA	Population database.	Database	2006-2009	66
16	Liu, et al	2015	(36)	Retrospective **cohort/registry** study	609	USA	Population database. Hospital and community	Database	2012-2013	65
17	Maurice, et al	2015	(160)	Retrospective **cohort/registry** study	189,768	USA	Population database	Database	2010-2011	Unknown
18	Womble, et al	2015	(152)	Retrospective **cohort/registry** study	682	USA	Population database. Hospital and community	Database	2012-2013	63
19	Loeb, et al	2016	(35)	Retrospective **cohort/registry** study	32,518	Sweden	Population database.	Database	2009-2014	67
20	Mishra, et al	2013	(34)	**Content analysis** of patient's internet conversations	464	USA	Internet conversations	Qualitative software – (Sentiment index)	2002-2012	Unknown
21	Ehdaie, et al	2017	(166)	Prospective **counselling intervention** to physicians	5 surgeons; 1,003	USA	Clinical/ Hospital	Database and Survey	2014-2015	60

					patients					
22	Venderbos, et al	2015	(197)	Retrospective **survey** comparing anxiety and distress at 0, 9 and 18 months on AS	150 (86%, 90%, 96% at 0, 9 and 18 months)	Netherlands	Clinical/ Hospital	Survey (CES-D Scale, MAX-PC, STAI-6, DCS)	2007-2008	Unknown
23	Venderbos, et al	2017	(182)	Retrospective **survey** comparing HRQoL in treatment groups: AS, RP, RT to matched patients	879 (65-75%)	Europe	Clinical/ Hospital	Survey (EPIC, SF-12, STAI-6, EQ-VAS)	2015	65 (AS), 66 (RT), 70 (RP)
24	Loeb, et al	2015	(108)	Retrospective **cohort/registry** study	11,726	Sweden	Population database	Database	2003-2007	64
25	Lang, et al	2017	(157)	Prospective **survey** to AS patients	531	USA	Clinical/ Hospital	Survey	2011-2012	Unknown
26	Hamdy, et al	2016	(107)	Prospective **cohort/registry** study	1643	UK	Clinical/ Hospital	Survey/Database	1999-2009	61
27	Kendel, et al	2016	(194)	Prospective **survey** study – men on AS and RP	316	Germany	Clinical/ Hospital	Survey	2008-2013	67
28	Vasaraine n, et	2012	(180)	Prospective **cohort/registry** study. HRQoL + drop-out	75,124	Helsinki	Clinical/ Hospital	Survey (RAND-36, IIEF-5, IPSS)	2006-2010	64
29	Bellardita, et al	2013	(175)	Prospective **cohort/registry** study. HRQoL and database AS adjustment analysis	103	Italy	Clinical/ Hospital	Survey/ Database (Mental health - symptom checklist-90, HRQoL – Prostate version)	2007-2012	67
30	Vanagas, et al	2013	(181)	Prospective **survey** study. HRQoL, anxiety and depression amongst AS, RP, RT, Chemo and HT	61/650	Lithuania	Clinical/ Hospital	Survey (EORTC, QLQ-C30)	2010-2011	>64

31	Hegarty, et al	2008	(176)	Retrospective **survey** of men on AS – to assess differences in HRQoL and anxiety and depression in men in the US and Ireland	29	USA and Ireland	Clinical/ Hospital	Survey (MUIS-C, UCLA-PCI, QLI)	Unknown	76
32	Smith, et al	2009	(185)	Retrospective cohort **registry** survey assessing AS HRQoL and cancer related data 3 years into an AS pathway	200/1647	Australia	Clinical/ Hospital	Survey/ Database (SF-12, IPSS)	2000-2002	63
33	Parker, et al	2016	(178)	Prospective cohort **survey** assessing HRQoL and anxiety in AS	180	USA	Clinical/ Hospital	Survey (EPIC, SF-12)	2006-2012	67
34	Punnen, et al	2013	(146)	Prospective cohort **survey**, assessing differences between RP and AS (at 1 and 3 years) in respect to HRQol, anxiety and depression.	122/679	USA	Clinical/ Hospital	Survey (PHQ-9, GAD-7)	2007-2010	60
35	Lane, et al	2016	(190)	Prospective cohort **survey** study, assessing HRQoL in AS, RP, RT	1438	UK	Clinical/ Hospital	Survey	1999-2009	61
36	van den Bergh, et al	2010	(186)	Prospective cohort **survey** study (PRIAS) assessing progression, HRQol, anxiety and depression and patient factors between men on AS, RP and RT.	129/150	Netherlands	Clinical/ Hospital	Survey (CES-D. STAI, SF-12)	2007-2008	65
37	Xu, et al	2011	(196)	Qualitative **interviews** with patients with LRPC	7 black men, 14 white men	USA	Clincal/ Hospital	Qualitative interview (thematically analysed)	Unknown	Unknown
38	Xu, et al	2016	(193)	Retrospective cross-sectional **survey**	266/391 (68%)	USA	Clinical/ Hospital	Survey	2009-2010	75
39	Wilcox, et al	2014	(177)	Prospective **survey** of men on AS – assessing HRQoL and anxiety and depression	47/61	Australia	Clinical/ Hospital	Survey (IIEF-5, IPSS, MAX-PC, UAS)	2013	62
40	Burnet, et al	2007	(187)	Prospective **survey** study assessing anxiety and depression in men on AS	100/329	UK	Clinical/ Hospital	Survey (HADS)	Unknown	67

41	Davison, et al	2011	(188)	Retrospective **survey** study to assess the support and information men require to sustain them while on AS.	25	Canada	Clinical/ Hospital	Survey (The control preferences scale)	2009-2010	64
42	Anderson, et al	2014	(189)	Prospective cohort **survey** study to assess anxieties in men AS and determine which of these anxieties predicted health-related quality of life (HRQL)	86	Australia	Clinical/ Hospital	Survey (HADS MAX-PC, FACT-P, STAI)	Unknown	66
43	Oliffe, et al	2009	(96)	A prospective **survey** study to describe the range of men's self-management strategies used to overcome AS-related uncertainty	25	Canada	Clinical/ Hospital	Survey	Unknown	Unknown
44	Berger, et al	2014	(198)	Retrospective **interview** study to generate hypotheses about the factors that influence patients' decisions to leave AS.	14/1159	USA	Clinical/ Hospital	Qualitative interviews (thematically analysed)	2010-2013	unknown
45	Seiler, et al	2012	(199)	Prospective cross-sectional **survey** study, to assess differences in anxiety and depression amongst couples	133	USA	Clinical/ Hospital	Survey	Feb 2010 – August 2010	66
46	Kinsella, et al	2015	(200)	Prospective education **intervention** to men on AS	117/244	UK	Clinical/ Hospital	Survey/ Database	2011-2012	63
47	Bokhorst, et al	2015	(204)	Retrospective **registry** study to determine the number of non-compliers with the follow-up protocol of the (PRIAS) study	4547	Netherlands	Population database	Database/ Registry	Unknown	66
48	Wade, et al	2015	(167)	A prospective cohort **survey** study assessing nurse-led AS clinics for accessibility, flexibility and level of support	85	UK	Clinical/ Hospital	Survey and interviews (thematically analysed)	2006-2008	64
49	Weerakoon, et al	2015	(43)	Retrospective **registry** study	1603	Australia	Population	Registry	2008-2012	66

50	Kazer, et al	2011	(116)	Focus group analysis of the needs of men on AS	7	USA	Research	Focus group	2009-2010	70
51	Wade, et al	2013	(167)	Prospective/Retrospective survey study	1144 (88-95%) at 7 and 35 days post biopsy	UK	Clinical/ Research	Survey HRQoL, HADS.	2006-2008	62
52	Wade, et al	2015	(99)	In-depth semi-structured interviews at 10 and 18 weeks post biopsy	85	UK	Clinical/ Research	Interviews (thematically analysed)	2006-2008	64
53	Latini, et al	2007	(195)	Retrospective survey study	105	USA	Registry/ Database	Survey 5-item fear of cancer re-occurance questionnaire	1997-2002	75
54	Jeldres, et al	2015	(179)	A prospective cohort survey using validated questionnaires	305	USA	Clinical/ Hospital	Survey (EPIC, RAND Medical outcomes short form, SF-36)	2007	65 (AS), 58 (RP)

Table 12 Purpose, Respondents, Explanation, Findings and Significance (PREFS) Checklist

Study, publication date	Quality Score	Purpose (P)	Respondents (R)	Explanation (E)	Findings (F)	Significance (S)	Category of paper
Davison et al, 2012, Canada	4	Yes	Yes	Yes	No	Yes	CO
Goh et al, 2012, USA	3	Yes	Yes	Yes	No	No	CO/Q
Orom et al, 2014, USA	4	Yes	Yes	Yes	No	Yes	CO
Xu et al, 2016, USA	4	Yes	Yes	Yes	No	Yes	CO
Orom et al, 2017, USA	4	Yes	Yes	Yes	No	Yes	CO
Anandadas et al, 2011, UK	3	Yes	Yes	No	No	Yes	SG
Gorin et al, 2011, USA	3	Yes	No	Yes	Yes	No	CO
Loeb et al, 2016, USA	3	Yes	No	Yes	Yes	No	Q
Volk et al, 2014, USA	3	Yes	Yes	Yes	No	No	Q
Xu et al, 2012, USA	3	Yes	No	Yes	Yes	No	Q
O'Callaghan et al, 2014, Australia	3	Yes	No	Yes	Yes	No	Q
Mishra et al, 2013, USA	3	No	No	Yes	Yes	Yes	SPO
Ehdaie et al, 2017, USA	4	No	Yes	Yes	Yes	Yes	SPO
Venderbos et al, 2015, Netherlands	4	Yes	No	Yes	Yes	Yes	SG
Venderbos et al, 2017, Europe	4	Yes	No	Yes	Yes	Yes	SG
Lang et al, 2017, USA	4	Yes	No	Yes	Yes	Yes	CO
Kendel et al, 2016, Germany	4	Yes	Yes	Yes	No	Yes	CO
Vasarainen et al, 2012, Helsinki	4	Yes	No	Yes	Yes	Yes	SG
Bellardita et al, 2013,4 Italy 4	4	Yes	No	Yes	Yes	Yes	SG
Vanagas, 2013, Lithuania	3	Yes	No	Yes	No	No	SG
Hegarty et al, 2008, USA and Ireland	3	Yes	No	Yes	Yes	No	SG
Smith et al, 2009, Australia	3	Yes	No	Yes	Yes	No	SG
Parker et al, 2016, USA	4	Yes	Yes	Yes	No	Yes	SG
Punnen, 2013, USA,	4	Yes	Yes	Yes	No	Yes	SG
Lane et al, 2016, UK	4	Yes	Yes	Yes	No	Yes	CO
Van den Bergh et al, 2010, Netherlands	4	Yes	No	Yes	Yes	Yes	SG
Xu et al, 2011,USA	4	Yes	No	Yes	Yes	Yes	Q

Study, publication date	Quality Score	Purpose (P)	Respondents (R)	Explanation (E)	Findings (F)	Significance (S)	Category of paper
Xu et al, 2016,USA	4	Yes	Yes	Yes	No	Yes	CO
Wilcox et al, 2014, Australia	4	Yes	No	Yes	Yes	Yes	SG
Burnet et al, 2007, UK	4	Yes	No	Yes	Yes	Yes	SG
Davison et al, 2011, Canada	3	Yes	No	Yes	No	No	CO
Anderson et al, 2014, Australia	3	Yes	Yes	No	No	Yes	SG
Oliffe et al, 2009, Canada	3	Yes	Yes	No	yes	No	CO
Berger et al, 2015, USA	3	Yes	Yes	No	No	Yes	Q
Seiler et al, 2012, USA	4	Yes	No	Yes	Yes	Yes	CO
Kinsella et al, 2015, UK	3	No	Yes	No	Yes	Yes	SPO
Wade et al, 2015, UK	3	Yes	No	Yes	Yes	No	CO/Q
Kazer et al, 2011 USA	4	Yes	No	Yes	Yes	Yes	Q
Wade et al, 2013, UK	3	Yes	No	Yes	Yes	No	SG
Wade et al, 2015, UK	3	Yes	No	Yes	Yes	No	Q
Latini et al, 2007, USA	4	Yes	Yes	No	Yes	Yes	CO
Jeldres et al, 2015, USA	3	Yes	No	Yes	No	Yes	SG
Donovan et al, 2016, UK	4	Yes	No	Yes	Yes	Yes	SG
Loeb et al, 2017, USA	33	Yes	No	Yes	Yes	No	Q
Le et al, 2016, USA	3	Yes	No	Yes	Yes	No	Q
Scherr et al, 2017, USA	3	Yes	No	Yes	Yes	Yes	Q/SG/CO
Taylor et al, 2017, USA	4	Yes	No	Yes	Yes	Yes	Q
Mader et al, 2017, USA	3	Yes	No	Yes	Yes	No	Q
Lyons et al, 2017, USA	2	Yes	No	Yes	No	No	Q
Chen et al, 2017, USA	4	Yes	Yes	Yes	Yes	No	CO

SG = standard gamble (HRQoL's), CO = contingent evaluation (survey), SPO = stated preference (other) - (monetary value or choices or ratings), Q = qualitative (interviews).

Table 13 Strength of confidence in quality of quantitative Cohort/Registry studies (Modified STROBE checklist)

Author and year	Variables documented			Bias		Statistical methodology			Descriptive data			Limitations	Score
	Outcome	Exposure	Confounders and modifiers	Documented	Addressed	Full description	Missing Data	Sensitivity analysis	Demographic	Clinical	Social		
Aizer, et al, 2012, USA	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	10
Loeb et al, 2013, Sweden	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Filson et al, 2014, USA	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	9
Hoffman et al, 2014, USA	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	9
Liu et al, 2015, USA	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	8
Maurice et al, 2016, USA	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	8
Womble et al, 2014, USA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Loeb et al, 2016, Sweden	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Loeb et al, 2015,Sweden	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	9
Hamdy et al, 2016, UK	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Bokhorst et al, 2015, Netherlands	Yes	Yes	Yes	No	No	Yes	No	No	No	Yes	No	Yes	6
Weerakoon et al, 2015Australia.	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	No	Yes	8
Parikh et al, 2017, USA	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	8
Bokhorst et al, 2016, Worldwide	Yes	Yes	No	No	No	Yes	No	No	No	Yes	No	Yes	5

Notes: variables (clear explanation of all outcomes, exposures, potential confounders and effect modifiers) data source (details given of measurement), study size (≥500 patients), bias (effort made to address potential sources of bias), statistical methodology (description of methods, missing data addressed, sensitivity analysis performed), descriptive data (characteristics of individuals given: demographic, clinical and social) and limitations (generalisability addressed, cautious interpretation).

Table 14 Summary table of determinants of choice and adherence to active surveillance among men with low-risk prostate cancer found in the systematic review

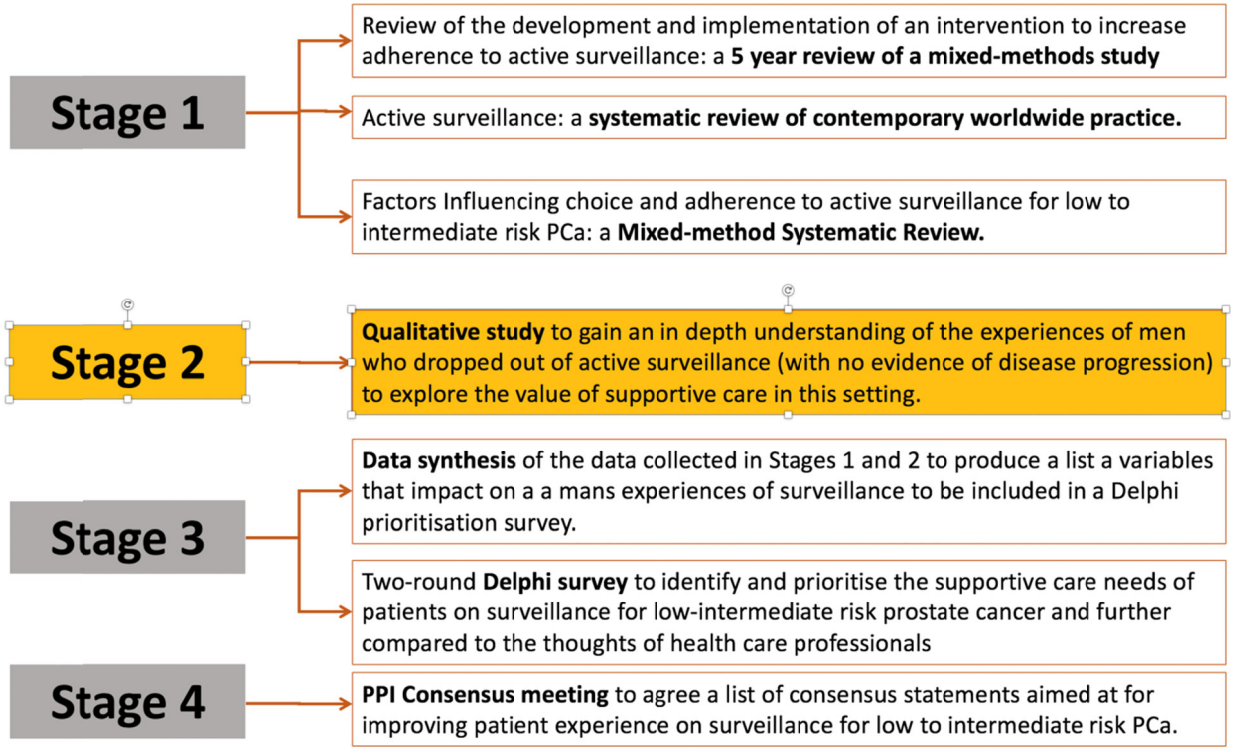
Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
1. Cancer characteristics	Cancer risk, stage, grade, PSA, tumour volume	Harmonizing national/local guidelines; Developing consensus-based appropriateness criteria	(31), (158), (36), (152), (112), (153), (37), (160), (35), (155), (159), (157), (33), (155), (108), (28), (154), (43)
2. Patient	Shared or collaborative role in decision-making; preferences; seeking information; feeling informed; knowledge	Shared decision-making; appropriate, reliable, and unbiased information; personal information; not contradictory and not stressful; increased availability of educational resources from trusted medical organizations for patients and families	(31), (33), (98), (32), (155)
	Patient characteristics (age, comorbidities, race, family history of prostate cancer, education, employment, insurance, socioeconomic status) and	Physician judgment and recommendation in shared decision-making with patient preference.	(31), (158), (36), (152), (112), (153), (37), (160), (35), (155), (159), (157), (33), (155), (108), (28), (154), (43)
	Impact of active treatment on: side-effects (urinary function, sexual function); preservation of HRQoL; time to accept diagnosis and to decide; “buying time”	Patient education and information	(31), (177), (34), (33), (28), (154), (32), (179), (175), (180), (190), (181), (176), (185), (155), (182)
	Self-management support; preference-style for diet, exercise and complimentary therapies; increased awareness and control of health; hope for prolonged and improved health; symptom monitoring; life-style	Patient education and information; self-management through diet and exercise, stress management, digital technology	(31), (33), (28), (98), (154)
	Preference for immediate cure; “cut it out”; desiring treatment efficacy/cure; avoid future regret	Patient education and information; supportive counselling	(28), (155), (157) (29), (195)
	Perceived cancer risk;	Patient education and information;	(33), (98), (155),

Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
	cancer worry; fear of disease progression; illness uncertainty; anxiety and distress	support; coping; manage anxiety; cognitive reframing; mindfulness; meditation; empowering; support groups; peer community; socialization; connect to others; shared activities; a sense of belonging; provide patients with a sense of meaning and control, robust monitoring processes, widespread agreement on monitoring process.	(29),(175), (31), (154), (158), (28), (32), (107, 166), (96), (177), (180), (178), (181), (186), (187), (146), (189), (193), (194), (199) (195), (196), (197)
	Monitoring stressors; Coping with anxiety, frequent PSA testing and repeat biopsies	Patient education and information; support; coping	(31), (33), (34) (175) (155), (167), (154), (28), (204)
	Awareness and acceptance of AS; survival expectation on AS	Availability of AS "success stories"	(34), (98), (96), (188), (193)
	Unknown factors	Qualitative interview studies with physicians and patients	(30), (28), (29), (33)
3. Family and social support	Advice/pressure from partner/spouse/children/ friends; marital status; family member with PC	Supportive counselling and information; patient not having to justify decision to others; support; education; reassurance	(31), (33), (29) (28), (32), (34), (198)
	Awareness and acceptance of AS	Public role models managed with AS and patient advocates	(28), (29), (33), (34), (198), (199)
	Fear of progression; disagreement about safety; preference to "eradicate the cancer"	Counselling and information; Enhanced recognition with information sources, treatment support, medical consultations	(29), (34), (33), (98)
4. Provider	Physician's recommendation; consistency in medical/nursing personnel	Training specialists to use a systematic approach to counselling patients about treatment options; communicating clearly and with confidence; using nudging narratives and framing techniques from behavioural science theory; maintain a positive and hopeful attitude; provide support and reassurance; public reporting of physicians' cancer management profiles	(31), (34), (28), (32), (159) (29), (107), (99), (30), (158), (36), (166), (33), (34), (98), (99)
	Specialty of physician giving treatment information	Multi-disciplinary team of specialists	(112), (31), (36)
	Provision of information and support	Provide and direct patients to accurate and unbiased information	(34), (200), (116), (31), (36), (28),

Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
		rather than describing AS as "doing nothing" or "no treatment" or scaring patients to active treatment, access to AS support groups. Establish consistency of support through nurse specialist roles.	(33), (96), (98), (116), (99)
	Physician attitudes; reluctance; concern about disease progression; perceived lack of data	Raise awareness, ongoing discussions at national meetings, quality improvement initiatives; having clear plans and stopping rules; systematic counselling on AS	(34), (30), (28) (166), (29), (33), (34), (169)
	Lack of availability of physicians recommending AS	Advocacy; subspecialty within urology	(28), (34)
	Confidence and trust in health professionals; closeness with physician; share control over treatment decision making	Improved community and medical education about treatment options, prognosis, side-effects; raise awareness of AS; consistent, unbiased treatment information; decisional support information; building trust in physician; patient trusting the physician's monitoring; patient feeling AS is an organized, supportive process;	(30) (33), (28), (169), (99)
5. Health care organization/practice	Urology practice site; hospital referral region; geographic region	Quality improvement initiatives to harmonize practice sites within networks	(36), (37), (160), (33), (34)
	Degree to which physician shared control over treatment decision making	System-levels determinants of trust, closeness and shared decision-making; organizational changes, e.g. longer consultation times	(169), (30), (28)
	Consultation at a multidisciplinary clinic; University hospital setting; academic hospital or high volume of PC patients	Multidisciplinary clinic may reduce the bias that specialists prefer the modality of treatment they themselves deliver and patients receive a balance perspective of risks and benefits of options	(112), (153), (160), (35), (37)
	Differences in surveillance strategies	National/International consensus of safe AS. Selection, monitoring and progression, patient information on large AS cohorts	(35), (36), (152), (43) (200), (204), (225)
6. Health policy level	Guideline recommendations	Harmonizing national/local guidelines; developing appropriateness criteria; national guideline recommending AS; real-time feedback to units on	(34), (35), (30)

Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
		adherence to national guideline in terms of annual report publicly available online	
	Trial/cohort data; year of diagnosis	Monitoring and future publications from on-going prospective protocol-based AS cohorts and registries	(34), (160), (35), (30)
	Awareness and acceptance	Guidelines; consensus; discussions at meetings; AS-specific billing code	(34), (30)

5. Chapter IV Stage 2: Qualitative study of semi-structured interviews



5.1. Introduction

On completion of the systematic review reported in chapter IV we identified a gap in the scientific literature. Despite worldwide documentation of high drop out from active surveillance without evidence of disease progression, only one study purposively included the opinions of these men (226). This phenomenon was most recently highlighted by an international collaboration; who, using Movember's Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) database (42), reported that 43.6% of men drop-out of active surveillance within 5 years of diagnosis with 12.8% converting to active treatment without evidence of disease progression. This study and others (6, 226) demonstrate the importance of understanding the reason for conversion to treatment (without evidence of

disease progression) in order to fully explore the requirements for supportive care aimed at increasing active surveillance adherence.

This chapter therefore describes the qualitative work undertaken as part of this project to gain further context and in depth understanding of the reasons why men with localised, low to intermediate risk prostate cancer drop out of active surveillance without evidence of disease progression, and to explore the value of supportive care in this setting, based on the conduct and analysis of semi-structured interviews.

5.2. Ethics

This study was approved by the Quality improvement Project Committee at The Royal Marsden NHS Trust (Appendix 10) as part of a wider project implementing a new information and supportive care programme for men on active surveillance.

5.3. Patients and methods:

Brinkman (in Kvale et al (227)) suggests that if one seeks to be familiar with how people understand their world, talking to them is the most appropriate method. Interviews are one of the most established and frequently used techniques for data gathering in this context (228). There are three different types of interviews: structured, unstructured and semi-structured. Structured interviews are based on questions that are asked of each and every participant. There is no variation in the questions between participants. Unstructured or informal conversation interviews have no predetermined set of questions (48, 90). Semi-structured interviews however, strike a balance between a structured interview and unstructured interview. They

allow for a flexible approach with minimum structure, but maximum depth in accordance with the principles of interpretive phenomenology (229), which aims to interpret the lived experience of the individual offering insights into how a given person, in a given context, makes sense of a given phenomenon.

Using the framework developed by Kallio and colleagues (230), I composed a semi-structured interview guide. These steps included; (1) identifying the prerequisites for using a particular interview technique; (2) retrieving and using previous knowledge; (3) formulating a preliminary semi-structured interview guide; (4) pilot testing the guide; and (5) presenting the complete semi-structured interview guide.

Having identified the prerequisites for using semi-structured interviews, I used the outcomes of my systemic review (Chapter IV) to develop an interview guide (Table 15). This guide was first piloted during four pilot interviews aimed at improving the instrumentation. The final guide was then submitted and reviewed by the expert Active Surveillance Reference Group for approval.

Table 15 Interview topic guide (derived from systematic review)

Category	Topic guide
Experience of prostate cancer diagnosis and treatment	Experience of diagnosis and treatment planning (perceptions and any concerns), Factual details of diagnosis, Reasons for choosing AS, Reasons for dropping out of AS , General facilitators and barriers whilst on AS
Patient factors	Perceived risk, Shared decision making ,Specific patient characteristics ,Lifestyle factors, Side effects, Preference
Cancer characteristics	Understanding progression, Stage, Gleason grade, PSA Tumour volume
Family and social support	Awareness + acceptance, Fear of progression Advice from family, friends and peer group
Provider	Speciality of clinician, Relationship with clinical team Availability of expertise in Active surveillance, Clinician recommendation, Information and support
Health organisation	Practice site, Differences/changes in AS strategy Multi-disciplinary clinic, Formal shared decision-making
Health policy	Guidelines, Trial and cohort data Awareness and acceptance by medical community

5.3.1. Sampling:

I used purposive sampling, a non-random method of obtaining a small group of people with specific characteristics is useful in naturalistic or qualitative research (233, 234). This method is specifically designed to garner depth and richness of experience (233). Participants were selected and approached according to both their experience of active surveillance and their willingness to share that experience (235).

5.3.2. Sample size:

In qualitative research, saturation is the most frequently touted guarantee of qualitative rigor offered by authors (235) with failure to reach saturation significantly impacting on the quality of the research conducted (236). However, saturation is defined within the literature in varying ways and is sometimes undefined (Table 16- (237)). Hence, Sandelowski (86)

proposed this to be at the judgement of the researcher and suggested that inexperienced researchers may need larger samples. In retrospect, I feel that saturation was achieved in this project after nine patient interviews, however, I continued to collect data for 14 interviews.

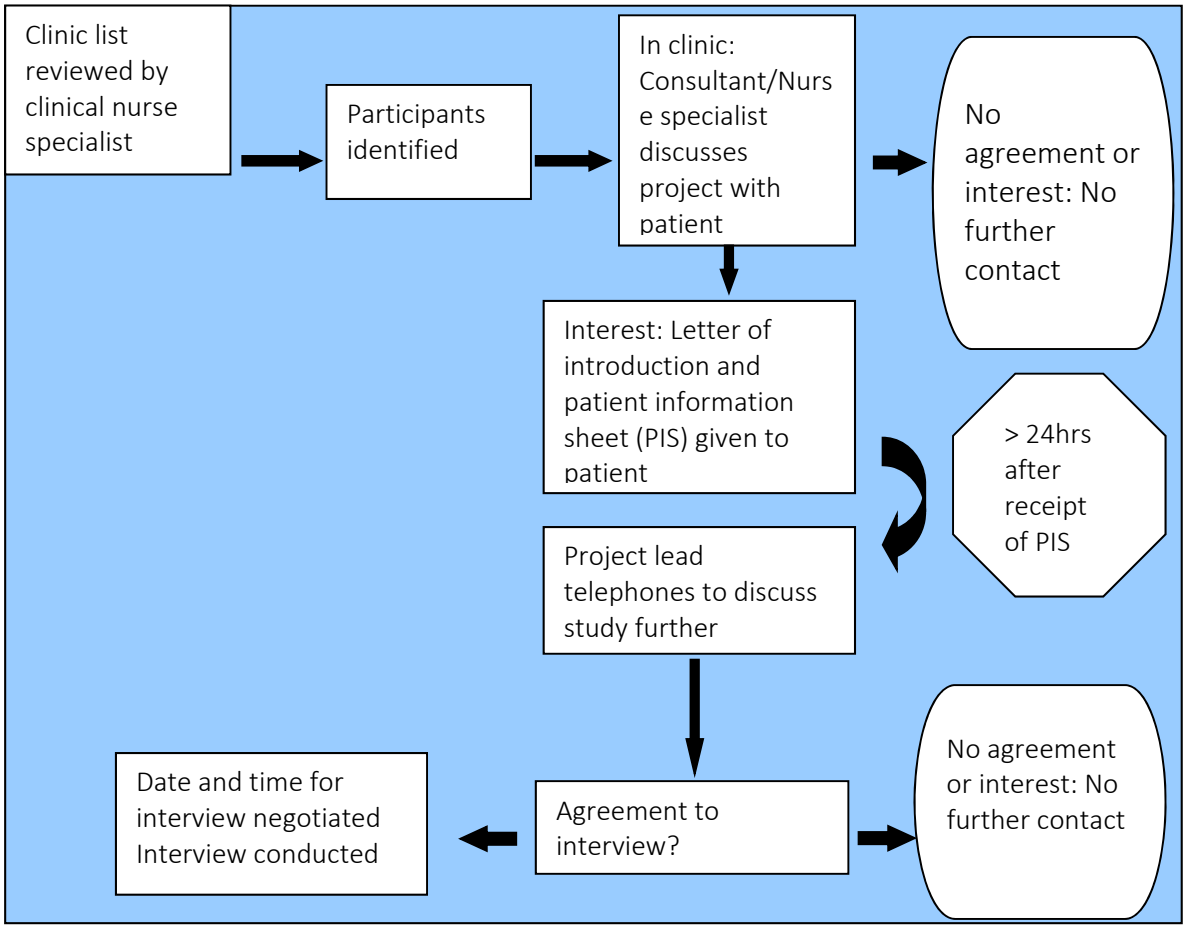
Table 16 Models of saturation and their principle foci (adapted from Saunders et al)

Model	Description	Principal focus
Theoretical saturation	Relates to the development of theoretical categories; related to grounded theory methodology	Sampling
Inductive thematic saturation	Relates to the emergence of new codes or themes	Analysis
A priori thematic saturation	Relates to the degree to which identified codes or themes are exemplified in the data	Sampling
Data saturation	Relates to the degree to which new data repeat what was expressed in previous data	Data collection

5.3.3. Selecting and recruiting patients

In accordance with the approval afforded through the Quality improvement project committee, the recruitment process involved more than one person and multiple stages (Figure 11). The Clinical Nurse Specialist reviewed consecutive appropriate clinic lists for all potential participants several weeks in advance of the clinic, this was then highlighted to the consultant who invited identified patients to take part by offering a patient information sheet (PIS) and a letter introducing the interviewer. In accordance with the principles of qualitative research and purposive sampling (51), anyone meeting the eligibility criteria was deemed an appropriate potential participant.

Figure 11 Recruitment process



5.3.4. Consent

An information leaflet describing the Quality improvement Project was offered to all participants (Appendix 11) and written consent was taken for each interview (Appendix 12) in accordance with the Department of Health research governance framework for health and social care (238).

5.3.5. Anonymity and confidentiality

For the purposes of this study, hard copy data were anonymised coded and kept in a locked cabinet. Electronic copies were stored alongside the identities of the participants securely

within a password-protected database. They were accessible only to the project team. Digital recordings were stored in password protected computer files, whilst the interview recordings were anonymised during the transcription process and then destroyed following analysis (239).

5.4. Pilot phase – Qualitative research skills

Experienced qualitative researchers suggest it is necessary to develop and enhance personal skills before conducting research interviews (227). Despite being an experienced nurse willing to discuss sensitive issues with people affected by cancer, I was conscious of the challenges of conducting a research interview as opposed to a clinical conversation. I was therefore cognisant of my need to actively facilitate a seamless transition from a clinical nurse to a nurse researcher. I conducted four pilot interviews with patients who had recently been recruited to the expert Active Surveillance Reference Group. These patients (the pilot group) had been on active surveillance for between 18 and 48 months.

Several issues were highlighted during the pilot phase including, length of time on AS, venue of interview and interview guide. As a consequence, only patients with more than 24 months experience of AS were subsequently invited to participate in this project, thus reducing the associated influence of an initial high drop-out rate noted around the first repeat biopsy and imaging (42).

The interview environment was also changed as a result of the pilot. The original pilot interviews were offered in either a clinic room or local coffee shop in-line with recommendations made by Clarke (240) who suggested that participants should be given a choice of venue and interviews conducted in a comfortable environment where seats are carefully arranged and there is suitable decor. However, both venues were found to lack in privacy which is consistent with recommendations by Burns and Grove (241), who suggested that interviews are held in a quiet, private room. The subsequent interviews were held in a private room in the patient advice and liaison offices.

5.4.1. Interview preparation

This pre-interview phase is important as the foundations for reciprocity are laid, positing that all participants will have a reason for being involved and, even if they are not conscious of it, want something in return (242). I therefore met each participant and answered any immediate questions allaying anxieties as well as inquiring after their journey. London transport was a recurring theme that acted as an 'ice breaker' with participants injecting humour into their stories. This topic allowed me to demonstrate my authenticity by sharing in their humour (228).

5.4.2. Conducting the interviews

Rose's (243) nine point checklist was used to initiate each interview.

Table 17 Interview checklist

	Checklist of points for explanation before an interview
1	Purpose of the interview
2	Clarification of topic under discussion
3	Format of the interview
4	Approximate length of interview.
5	Assurance of confidentiality
6	Purpose of digital recorder – ask permission to use it. Explain who will listen to the recording
7	Assure participant that he or she may seek clarification of questions.
8	Assure participant that he or she can decline to answer a question.
9	Assure participant that there will be opportunity during the interview to ask questions.

A semi-structured interview technique was then employed using open-ended questions, facilitated by the topic guide (227) (Table 15) which included: Recollection of their experiences of being diagnosed with prostate cancer, their perceptions of this process as well as any concerns, patients factors, cancer characteristics, family and social support, provider, organisational and policy issues.

Each interview lasted between 18 and 45 minutes and was conducted by myself, at the hospital. Despite introducing myself as the project lead, in more than half of the interviews the respondents directly asked about my professional background as a Nurse Consultant. My status as a Nurse would have had an influence on the nature of the interviews, and therefore

my values, assumptions, prejudices and influences were acknowledged (244) and considered in the analysis (245). The interviews were recorded and transcribed, as a 'clean verbatim' style with stutters, fillers and false starts omitted (246).

5.5. Analysis

Following a period of familiarization and immersion in the transcripts, analysis was undertaken in an inductive thematic manner in which all datasets were read and re-read in the search for emerging themes ('funnelling') (247), a coding structure was developed to facilitate this. A member of my thesis progression committee then independently applied the coding to one of the pilot interviews to ensure reliability, consistency and agreement. The application of the codes was discussed and arranged into patterns which were condensed into themes and discussed to challenge the analytical insights. This iterative process continued until consensus was reached and a coherent analysis was developed, an example of which can be seen in appendix 13.

To further validate these themes, respondent validation was carried out on three occasions, with a summary of the description of the key emergent themes sent to respondents for their comments. The respondents consistently endorsed the summary as accurately representing their views. Although this respondent validation suggested broad agreement (which was reassuring), it is acknowledged that the value of such an exercise can be limited by the respondents' reluctance to be overtly critical (248).

5.6. Results

5.6.1. Quantitative analysis

5.6.1.1. Patient demographics:

Participants were diagnosed at a single centre, and seen by the same Uro-oncology clinical team. Between June 2017 and February 2018, 18 men agreed to be interviewed about their experiences of active surveillance, with four later dropping out as a result of personal commitments. The resulting group of men (*n* = 14) were of varying age, background and ethnicity (Table 18) reflecting the local population. The mean age of participants in the interview study was 64.4years (49 to 76 years)

Table 18 Participant characteristics

	Age	Occupation	Ethnicity	Marital status
1	71	Retired garage owner	White European	Married
2	58	Teacher	White European	Widower
3	63	Builder	Asian	Married
4	61	Policeman	White European	Divorced
5	73	Retired carpenter	White European	Married
6	49	Salesman	White European	Single
7	66	Retired bank clerk	Black African	Married
8	72	Property developer	White European	Divorced
9	76	Retired bus driver	White European	Widower
10	55	Banker	White European	Married
11	66	Retired GP	Black Caribbean	Married
12	66	Charity executive	White European	Partnership
13	66	Retired factory foreman	Black Caribbean	Married
14	58	Journalist	White European	Divorced

5.6.1.2. Cancer characteristics:

All patients had been on AS for a mean time of 38.6 months (25- 63 months). Mean PSA was 5.1ug/l (2.1-8ug/l). 29% of participants were of black African, black Caribbean or Asian

ethnicity, which reflects the ethnic diversity of London according to the 2011 census (30%) (249) . The time interval between diagnosis and interview varied according to respondent, the influence of this delay was also considered in the analysis (Table 19).

Table 19 Participant cancer characteristics

	Age	PSA (at time of drop-out)	Gleason grade	T Score	Months on active surveillance
1	71	5.1	3+3	T2a	37
2	58	3.9	3+4	T2a	26
3	63	7.8	3+3	T2b	29
4	61	3.2	3+3	T1b	31
5	73	4.1	3+4	T2b	55
6	49	3.1	3+3	T1b	25
7	66	5.5	3+4	T2a	41
8	72	5.8	3+4	T2a	63
9	76	9	3+3	T1b	44
10	55	2.1	3+3	T1a	38
11	66	4.5	3+4	T2a	34
12	66	7.2	3+4	T2b	42
13	68	8	3+3	T2a	48
14	58	2.2	3+3	T2a	27

5.6.2. Qualitative data analysis:

The interviews revealed a range of recollections, feelings and opinions, which recurred over most of the interviews. These accounts have been grouped and described in the following themes:

i. Experience of diagnosis and subsequent consultations

ii. Shared decision making

iii. Supportive care and informational needs

iv. Administrative and organisational issues

v. Partner and peer support

5.6.2.1. Experience of consultations (diagnosis and follow-up)

The interviews highlighted aspects of experiencing diagnostic procedures; two men spoke about undergoing a biopsy as being among the most difficult aspects of their prostate cancer experience. AB said

> *'…you don't know what's going on' because there is no support until after the diagnosis. According to TF, in the waiting room, men were treated 'like a heard of cattle'…"*

Most participants commented that they found the diagnostic experience long and drawn out, making a direct comparison between the process of diagnosis and active surveillance.

> *"…At diagnosis my scan took three weeks and my biopsy results took four weeks. I almost missed my appointment because the letter arrived the morning of the appointment by which point I was climbing the walls….. It was just the same once I'd started on active surveillance – I couldn't deal with it…. "*

> *"Although active surveillance was attractive, I just couldn't go through the waiting every 12-18 months. It drove me crazy after the second lot of biopsies so I chose to have surgery. I just think they could sort this out so easily – its customer service. Good service and people are happy…"*

Other patients described later consultations as challenging with staff demonstrating poor communication skills with brief and/or dismissive interactions.

> *"…I was in and out in 5 minutes, I mean 5 minutes…, I'd barely sat down, to be told you've got cancer one week and then told you didn't need to worry about the next was beyond comprehension. Its cancer! Of course I was going to worry, he'd barely told me anything about monitoring. I wasn't really encouraged to ask questions….. I don't think these doctors appreciate that we haven't been to medical school, it's their job to help us understand…"*

> *"…When [the consultant] recommended AS, [my wife] and I, we made the decision on the spot, like, 'Yes, we'll do that'. I did get cold feet after it, and I rang [nurse] to run through the consultation again, to re-affirm to me that that was why he felt it was the best option. The nurse couldn't have been less interested. She asked why I was so rattled! I'd been on the phone for about 5 minutes when she said she'd have to go now as she had an urgent call to a patient that was in distress. I felt like a nuisance, I just wanted to scream at her that I had cancer too – I was distressed…"*

> *"…they were just so dismissive; the last straw was when a young doctor who wasn't much older than my grandson said… 'A man of your age, you can forget about it, you'll live another ten years'. And I said, 'Eh? What are you talking about it's bloody cancer!' I was so angry I then said, 'Fuck off! Well, wait until he gets to 70 and someone tells him that. My mother lived to 90, I don't see why I wouldn't too…"*

> *"…I was really fortunate, the nurse that I was introduced to spent about an hour with me on the phone the day after my hospital appointment. If she hadn't of phoned I don't know what I would have done. I just didn't understand what the doctor had told me. All I knew was I had cancer and it didn't need treating, I thought that meant that it was incurable!..."*

5.6.2.2. Shared decision making

The experience of shared decision making was described by many as limited.

> *"…It was confusing. I read that there were new guidelines on active surveillance and the doctor told me they weren't relevant to me as I was part of an active surveillance trial. I just wanted to discuss the implications of the guideline, was it better or worse than the care I was getting…"*

> *"…They didn't seem to want me to participate in the consultation; I felt as I they expected me to just agree to whatever they suggested, with the briefest of explanations. I'm a professional; I wouldn't expect my clients to agree to something just because I told them to do it. I think the NHS is out of step with the rest of the world in 2017!..."*

> *"… My neighbour was diagnosed with prostate cancer 6 months before me and he came here too. He had surgery. He went to an education class held by the nurses and spent quite a bit of time with his nurse talking about the treatment options. I was told the MDT had said I should be on surveillance. I didn't even know what an MDT was, and it wasn't explained! No options, no discussion, when I asked what else I could do, they said I didn't need to do anything. They didn't mention my bladder problems which is why I went to my GP in the first place…… it took 3 years and a visit to A and E before I got that sorted. I should have had my prostate out at the beginning…"*

5.6.2.3. Supportive care and informational needs

Participants made it clear that they needed information and support at all stages of their encounter with prostate cancer, this included: psychological support, descriptive

information, active surveillance research cohort data and self-care strategies. They also mentioned the need to talk rather than reading information.

> *"… Whilst there was plenty to read on the internet, it's finding people that have been through it that I found most helpful. … Often you can read and read but, at the end of the day, talking to someone, is the most important part…"*

A significant number of participants were not offered psychological support whilst on active surveillance, but felt that this was an important aspect of coping or adjusting to their diagnosis.

> *"…You try to keep things normal, but it isn't normal anymore … It's as normal as you can make things, but it isn't normal…I don't mean everything is an effort but there is a lot more thought having to be put into everything. I just needed someone to off-load on. I couldn't get through on the phone …. when I did, my nurse asked me what I was fussing over. I heard about the hospital psychological support services during my radiotherapy …. Too little, too late!..."*

> *"…I live on my own, and my close family live in the states. I really needed someone to talk to,…. you know… face to face. It's not the same on the phone..."*

> *"…I didn't want to make a fuss I knew other people were dying of cancer and I wasn't, I don't know why but that didn't make it any better…"*

> *"…I felt like I did when I went through my breakdown in 92, I'd lost control, I was spiralling. I think if they'd recognised this I could have got the help I needed…….. I saw my GP, he recommended that I had treatment – it was the best advice I'd been given since my diagnosis 3 years earlier, once I'd made the decision the weight lifted…"*

Participants also described a lack of enthusiasm from the clinical team for active surveillance;

> "…I asked the doctor for some references to the latest active surveillance research. He said there wasn't anything useful, he sounded so bored by the question. I did my own research; there was lots that interested me. I'm an engineer; I like to know how these things work. In my line of work if an engineer isn't engaged and interested in what he's doing mistakes happen, I couldn't risk it, it's my life…"

Several participants remarked on the difference in experience once they had chosen a treatment.

> *"…From the moment I choose active surveillance to the day I choose to have treatment I didn't see the consultant – that was 2 and a half years!..."*

> *"…I chose radiotherapy, from that moment I was introduced to my Nurse specialist and a support worker, I also met a specialist radiographer who was going to see me every week during my treatment. They sent me to a seminar…..where I met more of the team and lots of other patients….that was to prepare me for treatment. I couldn't have felt more love and support. I didn't feel nervous about the treatment at all. If they had done the same for surveillance I might not have had treatment…"*

5.6.2.4. Administrative and organisational issues

The administration of active surveillance was discussed by all participants, as a complicated process with no real oversight.

> *"…Suddenly he (the consultant) was interested in me. He said he would see me next time. In all the time that they were monitoring me (4 years) I'd only seen him once. It had been a different junior doctor every time. I just didn't have the confidence to go on*

with that…… If I'd seen him once a year even…… I think that would have been enough…"

"…I would go to the effort of re-organising my scans so that they fitted around my appointments as often the scan date fell after the appointment, and then the hospital would call or send a letter cancelling the clinic. … That's definitely an area they could improve: at least reassuring the patient that their scan was ok, instead of leaving them in limbo…"

The clinical nurse specialists were praised for their responsiveness but many felt they had little power to change the organisational model.

"…I called my nurse, she was lovely and apologetic but explained that there was no way of bringing my appointment forward as the scanner was back to back with people and the theatre lists were all full… It was good to know the situation but hardly reassuring. I remember that at least 2 of my scans were cancelled and my biopsy date was pushed back……. I felt like this was a big cancer centre trying to 'deal' with a group of patients that didn't fit the normal 'cancer patient' stereotype. I even heard people referring to us [patients on active surveillance] as the 'worried well'…"

Many of the participants suggested that a telephone call rather than an in-person appointment might be more efficient all round, as it felt like the process of active surveillance was less important than radical treatment.

"…the doctor said he would ring me in a couple of days. A week went by so I rang the hospital and asked what was going on. I was told that the doctor would call me as soon as he was available as the nurse 'wasn't allowed' to give results over the phone… I wasn't very happy with that, I felt that anybody facing a possible cancer diagnosis is going to be stressed….. so to leave me sitting there like a mug…"

"…When I had to go for the MRI scan, I would be very anxious waiting for those results because it often took weeks to hear from the hospital. I don't know how long it takes for someone to review these things but if they knew how we felt waiting perhaps it wouldn't take so long. I felt quite resentful, like my cancer was being de-prioritised because it didn't need treatment …"

5.6.2.5. Partner and Peer support

Participants also commented on the perception that men are unable to discuss *'personal'* issues with one another. They felt that this was perhaps an old stereotype perpetrated by the media rather than reality.

"…I even caught my wife saying it to our daughter. She said ' you know what men are like, he just won't talk about it', I did though, I just didn't know what to say to her. I wanted to chat to someone who was going through the same thing…"

They also reported actively challenging this by discussing their experience of prostate cancer with any men willing to listen, particularly at informal events but also increasingly over social media.

"…I'd never tweeted before but I'd had an account for a while… mainly to follow my kids. I decided to reply to a tweet from one of the cancer charities, when I did I was overwhelmed by the response and feeling of support…… I'm now tweeting about 3-4 times per day. I try to give support to others rather than getting into anything controversial, but it works, it helps, I feel better…."

Many felt that the opportunity to talk with other men in hospital (in waiting rooms, on wards etc.) could make a big difference to the active surveillance experience.

> *"…I went to the hospital with my mate, the waiting area had volunteers in it, they were chatting to people as they cane through the door and answering any questions. I found out that they'd all been diagnosed with cancer and treated at the hospital. One chap had had his prostate removed a few months before,. He couldn't stop praising the team, hospital and the experience. He looked so well, it spurred me on to having treatment. I think if I'd met someone that had been on surveillance for a few years I might have stuck with it…."*

> *"…Whilst there was plenty to read on the internet, … it's finding people that have been through it that I found most helpful. … Often you can read and read but, at the end of the day, talking to someone, is the most important part…"*

Several patients recognised the value of this interaction only after they had shared a hospital room with another man who had undergone surgery for their prostate cancer, commenting on how important this experience had been.

> *"….He really is one of my closest friends now. Having your prostate out is such a strange thing to bond over, but every appointment after our surgery we did together. It gives me a lift. I wish they'd had some way of putting men in touch with each other when I was diagnosed…"*

Some had even swapped numbers and kept in touch long-term.

> *"…We speak most weeks, and meet down the pub once a month. He's been my rock. The wife doesn't really understand, she just looked like she wanted to cry when I*

mentioned anything about having cancer. I think she was more relieved than me when I had the surgery…"

Partners represented a significant influence on participants decision to remain on active surveillance. Many described this as the most difficult element to balance.

"…My wife wanted me to have treatment, she never wavered. To be honest, she wore me down. I went for surgery because she wanted it, not because I did. If I'd been on my own I'd still be monitored…"

"…She just couldn't get her head around this surveillance thing. She kept saying its cancer, get rid of it. It became a big thing in our relationship, I remember it got so bad one day that she accused me of not loving her – wanting to die. It sounds crazy now, but it was driving us apart. I wanted her to come to my appointments to see how reassuring my diagnosis was, how low risk I was, … but she refused. I wish we'd had more time with the doctor and nurse at the beginning. I know she had questions, I think she was too scared to ask though…"

5.7. Discussion

My review of the scientific literature previously identified 5 themes that influence both choice and adherence to active surveillance in low to intermediate risk prostate cancer. These include; (1) patient characteristics (age, co-morbidities, knowledge, education, socioeconomic status, family history) and cancer characteristics (tumour grade, tumour volume, fear of progression/side-effects); (2) family and social support (advice, awareness and acceptance); (3) provider (specialty, communication, attitudes); (4) healthcare

organisation (geography, type of practice) and (5) health policy (guidelines, year, awareness) (95). However, only one of these studies included data collected from men who had dropped out of active surveillance.

This study therefore adds to the known body of literature by describing the perceived experiences of men diagnosed with localized prostate cancer who dropped out of active surveillance despite no evidence of progression. New findings to add to the known body of literature included; experiential factors associated with diagnosis and subsequent consultations, shared decision-making, supportive care and information needs, administrative processes and partner and peer support.

5.7.1. Diagnosis and subsequent consultations

Interviewing participants identified two aspects of their diagnosis and subsequent consultations that affected their experience of active surveillance, (i) communication and (ii) experience of diagnosis.

5.7.2. Communication:

Good communication skills in cancer care are key to achieving the important goals of the clinical encounter (250), which include (251, 252): establishing trust and rapport, gathering information from the patient and the patient's family, giving bad news and other information about the illness, addressing patient emotions and eliciting concerns. Moreover, informed consent to treatment and the patient's right to health care information and compassionate

care create ethical, legal, and humanistic mandates for competency in oncology communication (253). Therefore, communication initiated by the clinician providing opportunity for discussion about their cancer and the proposed treatment options, forms the basis of a confident relationship between patient and clinician and may also improve satisfaction with the care provided (254).

Research indicates that features of clinician–patient communication can predict health outcomes weeks and months after the consultation (255).

Pathways through which communication can lead to better health include; increased access to care, greater patient knowledge and shared understanding, higher quality medical decisions, enhanced therapeutic alliances, increased social support, patient empowerment, and better management of emotions (256). However, communication also affects health through a more indirect route through proximal outcomes of the interaction (e.g., satisfaction with care, motivation to adhere, trust in the clinician and system, efficacy in self-care, and shared understanding that can then affect health or contribute to the intermediate outcomes (e.g., adherence, and self-management skills) that lead to better health (257, 258). These proximal outcomes of effective communication are key to long-term adherence to active surveillance, suggesting clinicians involved in the management of these patients might benefit from enhanced communication skills training.

5.7.3. Experience of diagnosis:

In the early stages of a diagnosis, powerful social pressures place patients at a disadvantage in communicating honestly with their clinical team as maintaining a good relationship with one's doctor or nurse is given a higher priority than challenging the clinician (245), with a successful long-term outcome valued more highly than a satisfying process. However, when viewed in the context of active surveillance, a poor experience associated with the diagnostic phase could adversely influence both the initial selection and long-term adherence to active surveillance, where the process involves the same diagnostic tests to be frequently repeated to keep the patient "safe".

The recently published NHS long-term plan (259) has gone some way to shift the emphasis in cancer care to both early and rapid diagnostic pathways. However, strategies set up to expedite a diagnosis should also consider how they might incorporate a mechanism to mitigate the psychological morbidity of this stressful event. This would better reflect the experience of interview participants who identified and reported distress while they waited for their diagnosis undergoing a series of invasive tests over a protracted period of time, without access to any supportive care. Co-ordination between GPs and specialist hospital teams in developing a means of checking on patients' mental state and providing psychological support during diagnosis could minimise the distress associated with the diagnostic process (260) and ultimately reduce the psychological burden of selecting and adhering to active surveillance where diagnostic investigations are regularly repeated.

5.7.4. Shared decision-making

Although patients may vary in their interest in decision making, many value and seek involvement in the process (254). Where patients are not encouraged to be active participants, it is reported that their rates of treatment adherence suffer (261). However, striking the balance between being an active participant and taking responsibility for the result creates anxiety (262, 263) in patients and therefore clinicians should reflect on the subtleties of their consultations, creating an appropriate environment for shared decision making to flourish.

Participants in this study, described a process of adaptation to the status of ' prostate cancer patient' and an increased knowledge about their cancer and the treatment options evidently occurred over time. During this process, their orientation to participation in the planning of their cancer management also changed. As a result, more than two thirds of participants voiced that they had opted out of active surveillance as the clinical team had failed to respond to their changing needs. A willingness to vary our approach as health care professionals, calling on a range of styles, is demanding both in time and personal skills; however, sharing the principles of effective shared decision-making with our patients may be the key first stage.

5.7.5. Support and information:

There is clear disparity between the way that men with prostate cancer and healthcare professionals assess men's support and information needs whilst on active surveillance (264). In addition, individual patients differ in the amount of information and support that they

want to receive and clinicians fluctuate in how much they actually give. Information is undeniably a form of social support where successful. Effective management of information can increase satisfaction (265), facilitate participation in the consultation (266), increase the patient's ability to cope with illness (267), promote greater trust in clinicians (268) all of which can increase adherence behaviour (254).

Interview participants were particularly struck by the difference in information and supportive care when they decided to opt out of surveillance and undergo radical treatment (92). This is a result of a growing body of scientific evidence that supports the optimization of newly diagnosed cancer patients before starting treatment during a multimodal 'pre-habilitation' programme that includes physical and psychological assessment to establish a baselines functional level, identify impairments and provide information on self-management strategies that empower the patient and improve health through reducing the incidence and severity of treatment side effects (269).

However, perhaps of more relevance in respect to active surveillance is the recent research aimed at improving the quality of life of those living with and beyond cancer as part of a chronic care model (270). This model encourages high-quality care over six components: self-management support, delivery system design, decision support, clinical information systems, health care organization, and community resources (271, 272). When combined they have the potential to become a productive interaction between informed, activated patients and well-prepared, proactive healthcare teams. This approach is therefore one to consider where

active surveillance adherence is desired to reduce both the cost of unnecessary treatment and more importantly the physical and psychological burden of over-treatment.

Effective supportive care ultimately requires a multidisciplinary team approach (273), the members of which communicate with each other and the patient (264), enabling men to be confident that their care is coordinated and not disjointed. Supportive care is not, however, the province solely of health professionals but should be practised by all staff who come in contact with patients, including administrative and managerial staff. The practice of sensitivity, consideration, and professional warmth can make valuable contributions to patients' health and wellbeing whilst on long-term active surveillance whenever opportunities to answer questions, give information, counsel and listen occur (261).

5.7.6. Patient experience of administrative processes

Providing timely access to medical care is essential for both patient safety and positive health outcomes, therefore any delays as a result of healthcare processes can greatly affect patient experience and satisfaction (274). Healthcare providers and health systems need to make the care they provide more 'patient-centred' by ensuring that it is delivered in a way that fulfils patients' needs (275). This can be achieved by encouraging patients to play a more active role in this process (276).

Participants in this study highlighted the importance of efficient administrative processes for appointments and moving between services for example, imaging and biopsy, describing

uncertainty and disempowerment when appointments were delayed or cancelled. This reflects the views of participants in other tumour group studies, who when asked demanded new, efficient appointment processes and customer-care training for administrative staff. Managers and administrative staff to use values based performance tools to improve patients' experience plus changes to the structure of clinics to reduce waiting times, establishment of nurse-led end of treatment clinics, and digital access to records (277). The holy grail is therefore a positive therapeutic alliance which includes patients, family members, multiple health care professionals and administrative staff (274, 278). This alliance is 'therapeutic' because the quality of these relationships can affect health outcomes in two respects. First, a patient's perception that he or she has good care, will not be abandoned, and is understood can promote emotional well-being (279), Second, a patient's trust in his or her clinicians and the health care system can have an indirect effect through patient satisfaction with decisions, and patient commitment to a treatment plans (280). These factors are especially important in the case of active surveillance where patients consistently describe a lack of control and disempowerment (281).

5.7.7. Partner and Peer group support

Peer support is a widely accessed form of support for men with prostate cancer across the UK; with men reporting that peer discussions provide information, emotional support, and reduce feelings of social isolation (282). A suggested mechanism of effect for peer support is open discussion of problems in a supportive environment that promotes adaptation through peer learning and by facilitating cognitive and emotional processing (283).

Participant comments about the value of support given by their partners and peers was consistent with other studies suggesting an interaction between quality of relationships and cancer experience (284). Many participants commented that whilst on active surveillance they spent less time in hospital exposed to others in a similar situation and therefore missed out on the opportunity to talk with other men.

They also commented on the perception of men's inability to discuss *'personal'* issues with one another. They felt that this was perhaps an old stereotype perpetrated by the media rather than reality, reporting that they actively challenged this by discussing their experience of prostate cancer active surveillance with any man willing to listen, particularly at informal events but also increasingly over social media. Consideration should therefore be given to including partners and family in consultations (118, 285) and providing access to peer support opportunities through active surveillance support groups or web based groups(286).

5.8. Strengths and limitations

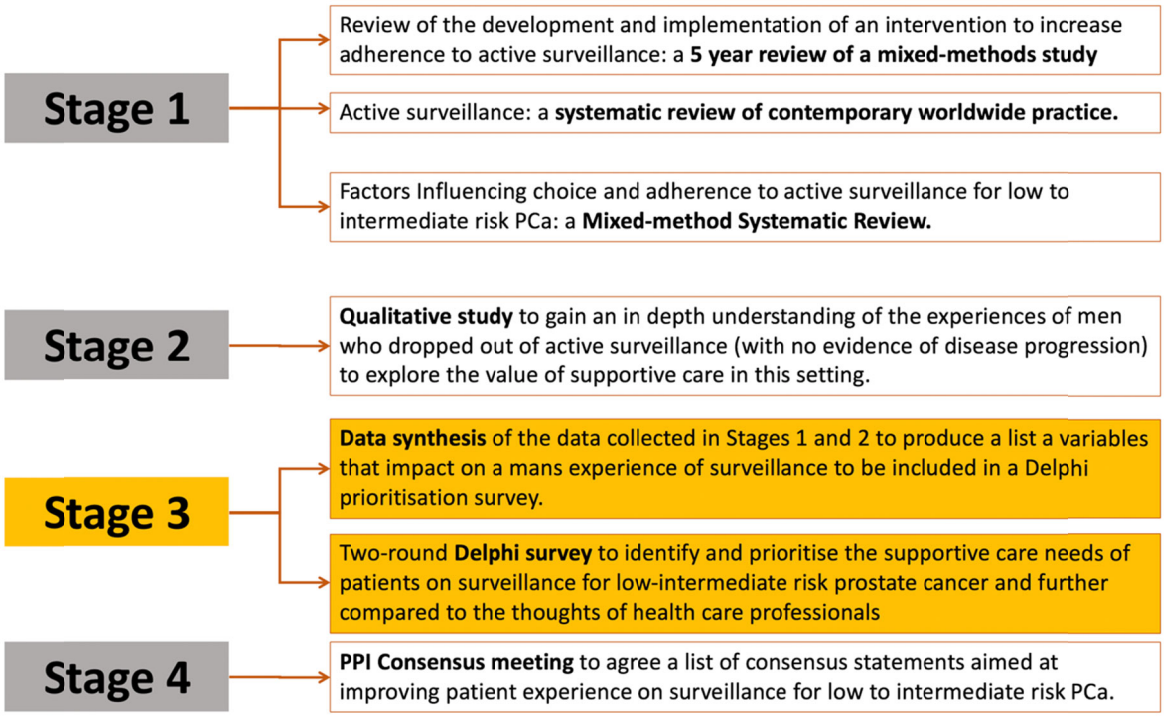
There are both strengths and limitations to this study; qualitative interviews rely on a respondents' ability to accurately and honestly recall details, thoughts, opinions, and behaviours. It is important to recognise that with the passage of time recollections and perceptions are often adjusted and re-appraised and as such these interview participants who all valued the importance of being seen as a 'good patient' (287) (not wanting to complain about their treatment whilst on active surveillance), might equally have valued being perceived as a 'good study, respondent' and tailored their accounts accordingly (245).

However, I believe the strengths outweigh the limitations. Qualitative interviews give participants the opportunity to elaborate in a way that is not possible with other qualitative methods such as survey research. They also enable the sharing of information in their own words and from their own perspectives rather than fitting those perspectives into limited response options. Also, we were able to observe and assess respondents body language which added richness and context to the data collected.

5.9. Conclusion

The experiences of men who dropped out of active surveillance without evidence of progression provides valuable insight into the changes required to improve men's experience and adherence to active surveillance.

6. Chapter VI Stage 3: The Delphi process: Identifying the supportive care needs of men on active surveillance



6.1. Part I – Data Synthesis

6.1.1. Introduction

Stage 3 of this project, aims to identify and prioritise the supportive care needs of men on active surveillance for low-intermediate risk prostate cancer using a modified Delphi technique. This modified Delphi method was positioned in a patient and public involvement (PPI) setting (288). Patient and Public Involvement research is carried out 'with' members of the public rather than 'to', 'about' or 'for' them (83). In healthcare studies, the term public is interpreted broadly to include potential patients, carers, family, people who use health services, organisations that support users of health services and other interested members of the community (84). This type of method helps to ensure inclusion of a wider range and larger sample size of opinion, whilst mitigating the bias of any individuals interpretation of

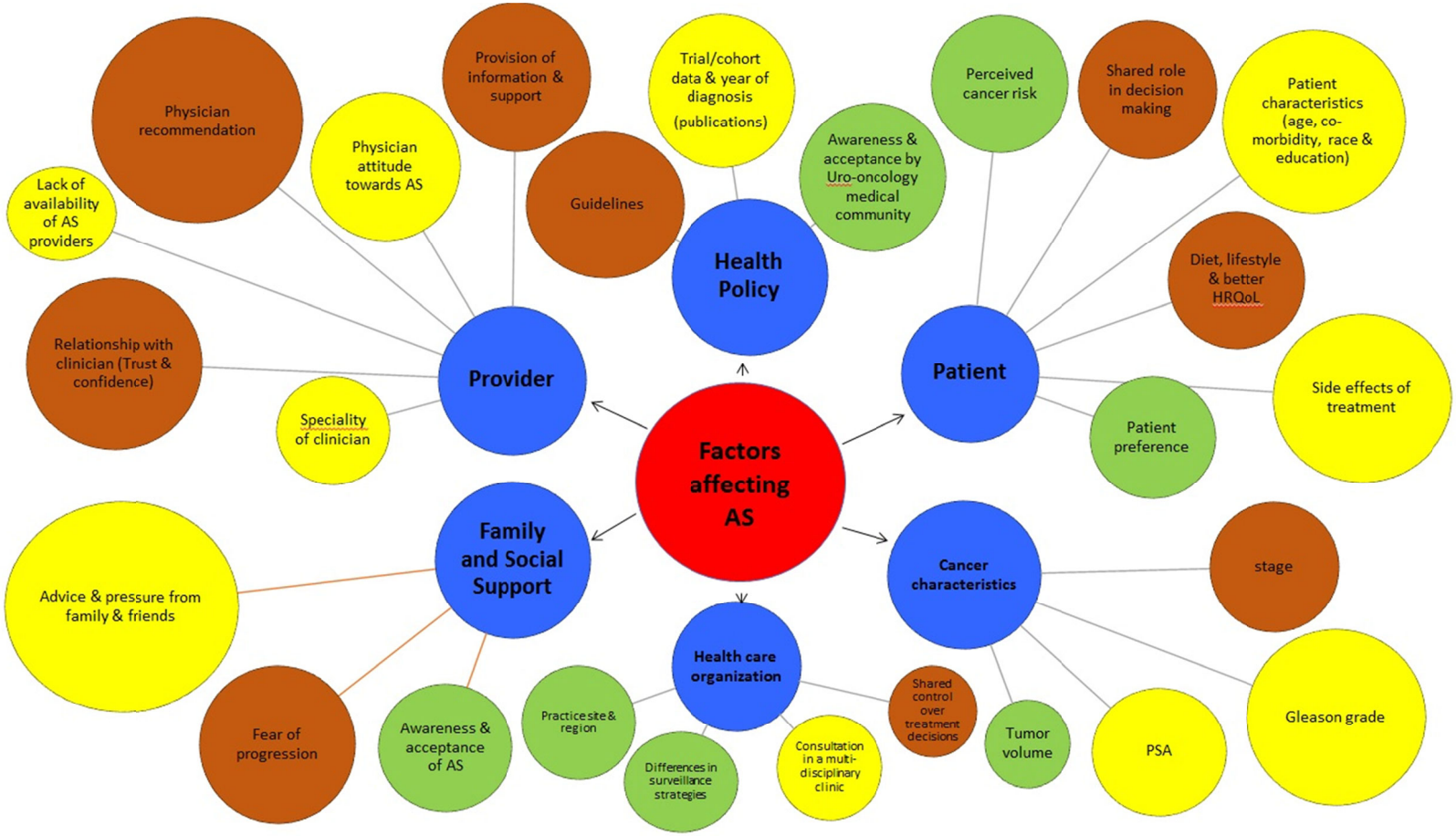
the previously collected data. It also allows for subjective statements made on a collective basis, and reduces domination by one person as is frequently found in focus groups.

6.1.2. Method

Analysis of the data collected in stages 1 and 2 was carried out in accordance with The Joanna Briggs Institute contingent framework (85). This framework involves two or more syntheses conducted sequentially based on results from the previous synthesis. This study began by asking a broad question "what factors influence choice and adherence to active surveillance" and is described in stage 1. This review generated a second research question, focused on the missing data from stage 1, describing the experience of men who opted out of active surveillance without evidence of cancer progression (phase X). Segregated syntheses were then conducted using a bayesian method, chosen as it allows the researcher to generate summative statements of the evidence through the meta-aggregation of data. All quantitative data collected during the course of the first stage was translated into qualitative description statements thus permitting meta-aggregation of the stage 1 and 2 data (86).

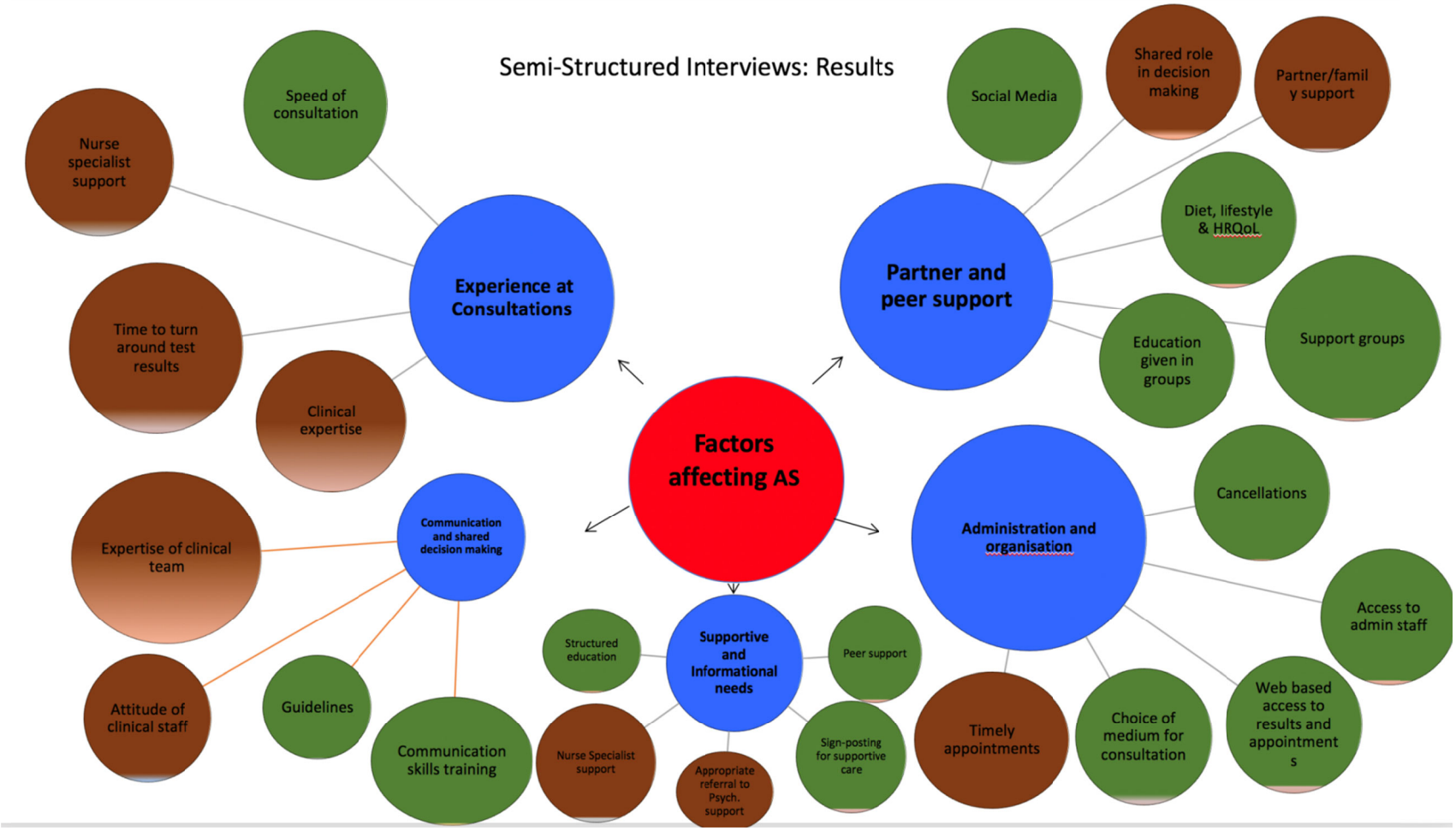
Figure 12, demonstrates a thematic representation of the results of the systematic review (stage 1), and Figure 13, represents the results of the semi-structured interviews (stage 2). Table 17represents the synthesis of these two datasets to be considered in the design of the Delphi surveys.

Figure 12 Systematic review results: Barriers and facilitators to AS choice and adherence; size of circle signifies the strength of evidence for each identified influencing factor.



Yellow circles = the evidence is strongest for active surveillance choice.
Green circles = the evidence is strongest for active surveillance adherence.
Brown circles = the evidence is relevant to both active surveillance choice and adherence.

Figure 13 Systematic review results: Barriers and facilitators to AS choice and adherence; size of circle signifies the strength of evidence for each identified influencing factor.



Green circles = the evidence is strongest for active surveillance adherence.
Brown circles = the evidence is relevant to both active surveillance choice and adherence.

Table 20 Synthesis of stage 1 and stage 2 data

Bayesian synthesis of determinants of choice and adherence to active surveillance among men with low-risk prostate cancer found as a result of the systematic review and interviews

Themes	Factors	Potentially targetable interventions for prioritisation	References + semi-structured interviews
1. Cancer characteristics	Cancer risk, stage, grade, PSA, tumour volume,	Harmonizing national/local guidelines; Developing consensus-based appropriateness criteria. Improving the experience of diagnostic pathway – waiting time, type of appointment, MDT recommendation	(31), (158), (36), (152), (112), (153), (37), (160), (35), (155), (159), (157), (33), (155), (108), (28), (154), (43)
2. Patient	Shared or collaborative role in decision-making; preferences; seeking information; feeling informed; knowledge	Shared decision-making; appropriate, reliable, and unbiased information; personal information; not contradictory and not stressful; increased availability of educational resources from trusted medical organizations for patients and families	(31), (33), (98), (32), (155)
	Patient characteristics (age, comorbidities, race, family history of prostate cancer, education, employment, insurance, socioeconomic status) and	Physician judgment and recommendation in shared decision-making with patient preference.	(31), (158), (36), (152), (112), (153), (37), (160), (35), (155), (159), (157), (33), (155), (108), (28), (154), (43)
	Impact of long-term AS on: (urinary function, sexual function); preservation of HRQoL; time to accept diagnosis and to decide; “buying time”	Patient education and information, “prostate’ health reviews at consultations	(31), (177), (34), (33), (28), (154), (32), (179), (175), (180), (190), (181), (176), (185), (155), (182)

Themes	Factors	Potentially targetable interventions for prioritisation	References + semi-structured interviews
	Self-management support; preference-style for diet, exercise and complimentary therapies; increased awareness and control of health; hope for prolonged and improved health; symptom monitoring; life-style	Patient education and information; self-management through diet and exercise, stress and anxiety management, digital technology.	(31), (33), (28), (98), (154)
	Preference for immediate cure; "cut it out"; desiring treatment efficacy/cure; avoid future regret	Patient education and information; supportive counselling	(28), (155), (157) (29), (195)
	Perceived cancer risk; cancer worry; fear of disease progression; illness uncertainty; anxiety and distress	Patient education and information; support; coping; manage anxiety; cognitive reframing; mindfulness; meditation; empowering; support groups; peer community; socialization; connect to others; shared activities; a sense of belonging; provide patients with a sense of meaning and control, robust monitoring processes, widespread agreement on monitoring process.	(33), (98), (155), (29),(175), (31), (154), (158), (28), (32), (107, 166), (96), (177), (180), (178), (181), (186), (187), (146), (189), (193), (194), (199) (195), (196), (197)
	Monitoring stressors; Coping with anxiety, frequent PSA testing and repeat biopsies	Patient education and information; support; coping	(31), (33), (34) (175) (155), (167), (154), (28), (204)
	Awareness and acceptance of AS; survival expectation on AS	Availability of AS "success stories"	(34), (98), (96), (188), (193)
	Unknown factors	Qualitative interview studies with physicians and patients	(30), (28), (29), (33)
3. Family and social support	Advice/pressure from partner/spouse/children/friends; marital status; family member with PC	Supportive counselling and information; patient not having to justify decision to others; support; education; reassurance	(31), (33), (29) (28), (32), (34), (198)

Themes	Factors	Potentially targetable interventions for prioritisation	References + semi-structured interviews
	Awareness and acceptance of AS	Public role models managed with AS and patient advocates	(28), (29), (33), (34), (198), (199)
	Fear of progression; disagreement about safety; preference to "eradicate the cancer"	Counselling and information; Enhanced recognition with information sources, treatment support, multi-disciplinary consultations (Doctor and Nurse), expert patients, Peer group meetings (support)	(29), (34), (33), (98)
4. Provider	Physician's recommendation; consistency in medical/nursing personnel	Training specialists to use a systematic approach to counselling patients about treatment options; communicating clearly and with confidence; using nudging narratives and framing techniques from behavioural science theory; maintain a positive and hopeful attitude; provide support and reassurance; public reporting of physicians' cancer management profiles	(31), (34), (28), (32), (159) (29), (107), (99), (30), (158), (36), (166), (33), (34), (98), (99)
	Specialty of physician giving treatment information	Multi-disciplinary team of specialists	(112), (31), (36)
	Provision of information and support	Provide and direct patients to accurate and unbiased information rather than describing AS as "doing nothing" or "no treatment" or scaring patients to active treatment, access to AS support groups. Establish consistency of support through nurse specialist roles, type of education offered, expert patients	(34), (200), (116), (31), (36), (28), (33), (96), (98), (116), (99)
	Physician attitudes; reluctance; concern about disease progression; perceived lack of data	Raise awareness, on-going discussions at national meetings, quality improvement initiatives; having clear plans and stopping rules; systematic counselling on AS	(34), (30), (28) (166), (29), (33), (34), (169)
	Lack of availability of physicians recommending AS	Advocacy; subspecialty within urology	(28), (34)
	Confidence and trust in health professionals; closeness with	Improved community and medical education about treatment options, prognosis, side-effects; raise awareness	(30) (33), (28), (169), (99)

Themes	Factors	Potentially targetable interventions for prioritisation	References + semi-structured interviews
	physician; share control over treatment decision making	of AS; consistent, unbiased treatment information; decisional support information; building trust in physician; patient trusting the physician's monitoring; patient feeling AS is an organized, supportive process;	
	Administration of surveillance pathway	Waiting times, administrative access, appointment type, web based organisation of bookings and cancelations, biopsy and imaging management and results review	Semi-structured interviews
5. Health care organization/practice	Urology practice site; hospital referral region; geographic region	Quality improvement initiatives to harmonize practice sites within networks	(36), (37), (160), (33), (34)
	Degree to which physician shared control over treatment decision making	System-levels determinants of trust, closeness and shared decision-making; organizational changes, e.g. longer consultation times	(169), (30), (28)
	Consultation at a multidisciplinary clinic; University hospital setting; academic hospital or high volume of PC patients	Multidisciplinary clinic may reduce the bias that specialists prefer the modality of treatment they themselves deliver and patients receive a balanced perspective of risks and benefits of options	(112), (153), (160), (35), (37)
	Differences in surveillance strategies	National/International consensus of safe AS. Selection, monitoring and progression, patient information on large AS cohorts	(35), (36), (152), (43) (200), (204), (225)
6. Health policy level	Guideline recommendations	Harmonizing national/local guidelines; developing appropriateness criteria; national guideline recommending AS; real-time feedback to units on adherence to national guideline in terms of annual report publicly available online	(34), (35), (30)
	Trial/cohort data; year of diagnosis	Monitoring and future publications from on-going prospective protocol-based AS cohorts and registries	(34), (160), (35), (30)
	Awareness and acceptance	Guidelines; consensus; discussions at meetings; AS-specific billing code	(34), (30)

6.2. Part II –Delphi Prioritisation Survey

6.2.1. Subjects and methods:

Following synthesis of the results determined by the systematic literature review and patient interviews describing the views and experiences of men who had opted out of active surveillance with no evidence of cancer progression. Sixty-nine items were considered for development into survey statements (Table 20).

The draft items were presented and discussed at the expert Active Surveillance Reference group (ASRG) meeting. The ASRG consisted of seven patients, five HCPs (clinical oncologists, urological surgeon and nurse specialists) as well as a patient and public involvement specialist and was established to guide the project from design to end through regular virtual meetings. The group reviewed the proposed list of statements, also providing guidance on the language to be employed in the survey (288). The Heath care professional survey and PPI survey were written with different language to describe the same items (appendix 14 & 15). Consensus was reached on the inclusion of 62 question statements.

Health care professional (HCP) participants were recruited via social media, through twitter and with the assistance of the British Association of Urological Surgeons, British Association of Urology Nurses, the British Uro-Oncology Group and Specialist Urology Registrar Group. Patient and partners were recruited through The Royal Marsden, Epsom and St Helier and King's College Hospital prostate cancer clinics.

A two-round modified Delphi survey was conducted over an eight week period, the maximum suggested timeframe (288) to ensure continued engagement by participants. The first survey was live for two weeks, followed by a two week analysis period. Round 2 was launched and available for four weeks. The survey was presented to participants in block-randomisation format to avoid the influence of respondent's willingness, 'context effect' or motivation to complete the survey (289-291).

Survey completion was anonymous; however, demographic information was collected. Patients were asked to provide their age, level of education, relationship to AS (e.g. patient, partner, and family member) and number of months on AS (where appropriate). Healthcare professionals were asked to provide their age, area of the country practising and current profession. The questionnaire was administered through the General Data Protection Regulation (GDPR - 2018) (292) compliant smart survey website.

Participants were asked to score each item on a scale from 1 (not important) to 7 (most important). The first round of the questionnaire allowed participants to add further items as free text. , The second round included additional items. The results of the first round of the survey were reviewed and fed back to participants before completing the second round. We specifically informed participants about the items that were ranked in the frst round bu participants as a priority (score of ≥6) by >70%. Items scoring ≥6 by >70% of participants for each round within the stakeholder groups were selected for the consensus meeting.

6.2.2. Results: Healthcare professional characteristics:

114 health care professionals took part in the Delphi-survey. 71% of whom were 49 years of age or under and 79% were doctors. The demographic of participants that registered suggested that over half (52%) were clinically active in the south of England; however 13% of participants practised outside of the UK (Table 21).

Table 21 Healthcare professional Survey participant characteristics

Age Range	No. of participants
20-29	1
30-39	40
40-49	40
50-59	19
60-69	12
Profession	
Consultant	65
Hospital Trainee	25
GP	0
GP Trainee	0
Nurse	23
AHP	1
Practice area	
Midlands	2
North of England	10
South of England	59
Scotland	2
Wales	3
Europe	10
Rest of the World	5
Anon	23

6.2.2.1. Patient and public participant characteristics

55 people took part in the survey. Participants included 36 men currently on active surveillance, 16 partners/family of men on active surveillance and 3 men that were previously on active surveillance. The median time that participants had been on active surveillance was

24 months (range: 6-156 months). 73% of participants over ≥ 60years of age and were predominantly of White British heritage. 71% of participants had at least a University Diploma or Degree (Table 22).

Table 22 PPI Survey participant characteristics

Age Range	No. of participants
0-19	0
20-29	1
30-39	0
40-49	5
50-59	9
60-69	22
70-79	17
80+	1
Ethnicity	
White other	1
White British	45
White Irish	3
Asian	3
Black African/Caribbean	3
Level of education	
School	5
Vocational qualification	2
College	9
University Diploma/Degree	19
University Higher Degree	20

6.2.2.2. Survey results:

The survey was administered in blocks of questions in line with the themes identified during stage I and II; (1) Patient factors, (2) Cancer factors, (3) Healthcare provider factors, (4) Healthcare organisation factors, (5) Support and Information factors, (6) Follow-up factors.

We compared the level of agreement between PPI and HCP survey responses by identifying all items where >70% of respondents scored the item as ≥ 6 (6 = much more important, 7 =

most important) (Table 23 to Table 29). Removing the respondents working outside of the UK made no significant difference to the results and therefore these responses were included in the final analysis. The items are ordered in accordance with the priorities of the PPI group. The items depicted in red represent no consensus between the stakeholder groups.

6.2.2.2.1. Patient factors

There was general agreement in relation to patient factors, however, the second highest priority identified by the PPI group was access to reliable sources reporting on the latest research in AS, which in contrast did not appear at all on the HCP priority list. In contrast, HCPs suggested that partner/family acceptance of AS was one of the top 5 issues for men on AS (79%), however a more moderate 67% of the PPI group agreed this was of significant influence (Table 23).

Table 23 Prioritisation of Patient factors

	Patient factors			
	Items prioritised by PPI	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Feeling involved in decisions about active surveillance e.g. scans and re-biopsy	89	The patient feeling involved in decisions about monitoring active surveillance	90
2	Access to reliable sources reporting on the latest research in prostate cancer and active surveillance	84	Access to reliable sources reporting on the latest research in prostate cancer and active surveillance	59
3	Good mental health whilst on active surveillance	82	Quality of mental health whilst on active surveillance	77
4	Good physical health whilst on active surveillance	81	Quality of physical health whilst on active surveillance	80
5	Recommendation from the hospital clinical team	79	Recommendation from the hospital clinical team	85
6	Partners/family awareness and knowledge of active surveillance	72	Partners/family awareness and knowledge of active surveillance	79
7	Including partner/family in consultations and cancer decisions	70	Including partner/family in consultations and cancer decisions	82
8	Partners/family acceptance of active surveillance	67	Partners/family acceptance of active surveillance	79

6.2.2.2.2. Cancer factors

The top 3 cancer factors identified by the PPI group were similarly recognised by HCPs. The HCP group felt that understanding of Gleason grade (72%), PSA (83%) and MRI (74%) were significant, whereas the PPI group found these items less important with 65%, 67% and 61% of participants, respectively, rating their value as a significant (Table 24).

Table 24 Prioritisation of cancer factors

	Cancer Factors			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Understanding the risk of prostate cancer progressing	81	Understanding the risk of prostate cancer progressing	94
2	Understanding the other treatment options for prostate cancer	72	Understanding the other treatment options for low-intermediate risk prostate cancer	90
3	Understanding prostate cancer	70	Understanding prostate cancer	91
4	Understanding the pathology of prostate cancer (Gleason grade)	65	Understanding the pathology of prostate cancer (Gleason grade)	72
5	Understanding the role of PSA in active surveillance	67	Understanding the role of PSA in active surveillance	83
6	Understanding MRI scans and the role they play in active surveillance	61	Understanding MRI scans and the role they play in active surveillance	74
7	Control of health - including regular assessment of any prostate related symptoms e.g. urinary symptoms	70	Control of health - regular assessment of prostate related symptoms e.g. urinary symptoms	73

6.2.2.2.3. Healthcare provider factors

PPI and HCP participants agreed on the top 3 items of significance importance. HCPs suggested an additional 3 items were significant: ease of access to the clinical team (87%), regular contact with the clinical team (77%) and clinical team support for AS (92%), however none of these factors were significant to the PPI group (Table 25).

Table 25 Prioritisation of Healthcare provider factors

	Healthcare Provider			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Consistently seeing the same clinical team (doctor or nurse)	79	Consistently seeing the same clinical team (doctor or nurse)	83
2	Access to reliable information about active surveillance	74	Access to reliable information about active surveillance	91
3	Sharing treatment decision making with the clinical team	72	Sharing treatment decision making with the clinical team	88
4	Easy access to the clinical team	67	Easy access to the clinical team	87
5	Regular contact with the clinical team (nurse or doctor) via phone	44	Regular contact with the clinical team (nurse or doctor) via phone	77
6	The clinical team supporting and recommending active surveillance	63	The clinical team supporting and recommending active surveillance	92

6.2.2.2.4. Healthcare organisation factors

There was general agreement across this section of items, although HCPs felt that administrative issues may significantly influence AS adherence (75%). This was not reflected in the PPI survey, where this was rated of low significance (39%). However, when asked specifically about the cancellation of appointments, scans or biopsies this was reported by both stakeholder groups as a barrier to active surveillance adherence (70% of the PPI group and 71% of the HCP group) (Table 26).

Table 26 Prioritisation of Healthcare organisation factors

	Healthcare Organisation			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Agreement on guidelines for safe active surveillance	79	Clear National or Local guidelines for safe active surveillance	78
2	Difficulty contacting the clinical team	79	Difficulty contacting the clinical team	82
3	Difficulty contacting the administrative team	39	Difficulty contacting the administrative team	75
4	Being monitored by a team/clinician with a special interest in active surveillance	77	Being monitored by a team/clinician with a special interest in active surveillance	75

6.2.2.2.5. Support and Information

There was agreement between PPI and HCP respondents in reference to support and information, where it was felt that support and information should be delivered by a healthcare professional. The PPI group reached consensus in the content of the information they required which included exercise and lifestyle advice, as well as stories relating to public role models (Table 27). However, no consensus was reached on the method of delivery at this stage, with equal weighting given to webinars, seminars and printed information (Table 28).

Table 27 Prioritisation of Support and Information factors

	Support and Information			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Education delivered by a health care professional (doctor, nurse, physio etc)	77	Education by a health care professional (doctor, nurse, physio etc)	81
2	Exercise advice	71	Exercise advice	43
3	Lifestyle advice	72	Lifestyle advice	49
4	Public role model stories	70	Public role model stories	59

Table 28 Prioritisation of method of follow-up

	Follow-up method			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Face to face "information and support seminar" given to a group of men on active surveillance (hospital base)	31	Face to face "information and support seminar" given to a group of men on active surveillance (hospital base)	31
2	Face to face "information and support seminar" given to a group of men on active surveillance (community space)	26	Face to face "information and support seminar" given to a group of men on active surveillance (community space)	18
3	Online website (webinar)	22	Online website (webinar)	12
4	Printed information	21	Printed information	39

6.2.2.2.6. Follow-up factors

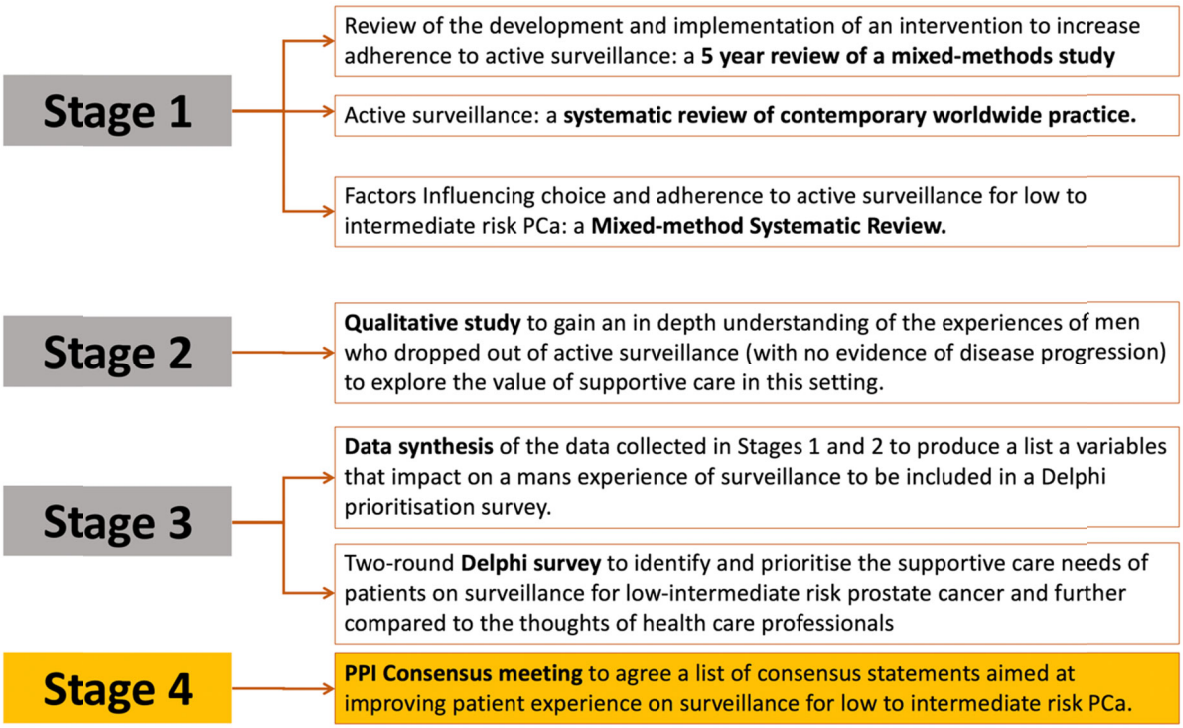
In reference to follow-up, there was no specific agreement between PPI and HCP groups. The PPI group felt that the only important aspect of follow-up was being seen face to face,

whereas the HCP group were more concerned that patients received consultation from a hospital doctor, nurse specialist and/or were seen in a specialist AS clinic. PPI agreement on these three factors was moderate to low with 60%, 47% and 58% agreement of importance respectively (Table 29).

Table 29 Prioritisation of follow-up factors

	Follow-up			
	Items prioritised by Patients	% of respondents ≥ 6	Items prioritised by Health care professionals	% of respondents ≥ 6
1	Face to face appointments	82	Face to face appointments	67
2	Offered my preferred method of contact for follow-up	81	Offered my preferred method of contact for follow-up	59
3	Follow-up by a hospital doctor	60	Follow-up by a hospital doctor	71
4	Follow up by a Specialist Nurse	47	Follow up by a Specialist Nurse	87
5	Seen in a specialist active surveillance clinic	58	Seen in a specialist active surveillance clinic	78

7. Chapter VI Stage 4: Active surveillance reference group consensus



7.1. Introduction

The following chapter describes the process of consensus that was achieved during a meeting of the expert Active Surveillance Reference group (ASRG). The objective of the meeting was to agree on the priorities for supportive care, to translate these into useable consensus statements to inform the development of any future active surveillance interventions.

7.2. Results of the ASRG consensus meeting

Following completion of the two round prioritisation survey, the ASRG was invited to participate in a face-to-face consensus meeting held on 17th December 2018.

This meeting was based on the nominal group technique (NGT), which is a highly structured face-to-face group interaction to empower participants to provide an opportunity to share their opinions with other members. The meeting was moderated by an independent expert in consensus methods to ensure that all participants were encouraged to provide an opinion.

For the purposes of this project, we set out to follow Ulschak's (73) recommendation that using a seven point Likert scale, 80% agreement was required. However, few items achieved 80%, and therefore it was agreed by the Active Surveillance Reference Group that a 70% agreement rate was reasonable.

28 statements were identified as scoring ≥6 by >70% of participants, as a result of the two survey rounds. The ASRG were then requested to rank the statements in each theme from most important to least important, and provide their respective reasoning (293). Following mediated discussions, 24 consensus statements were formulated on the basis of these results. These statements were allocated across four themes; (1) Principles of an active surveillance programme (Table 30), (2) Structure of consultations (Table 31), (3) Content: Information and Support (Table 32), (4) Delivery of information (Table 33).

7.3. Consensus statements for active surveillance information and supportive care needs:

Table 30 Principles of an active surveillance programme

	Principles of an active surveillance programme
1	Promote good physical health whilst on active surveillance
2	Promote good mental health whilst on active surveillance
3	Develop nationally agreed guidelines for safe active surveillance
4	Ensure all patients have easy access to the clinical team (nurse or doctor)
5	Provide access to exercise advice from a professional (in relation to prostate cancer)
6	Provide access to lifestyle advice from a professional (in relation to prostate cancer)

Table 31 Structure of consultations

	Structure of consultations
1	Offer the appointment type that best suits the patient e.g. telephone, face to face, skype
2	Offer patients their preferred contact method for appointments and outcome of consultations (email, text, letter, phone)
3	Ensure patients are consistently seen by the same clinical team (doctor or nurse)
4	Include regular assessment of prostate related symptoms e.g. urinary symptoms, erectile function
5	Offer active surveillance monitoring by a clinical team with a special interest in active surveillance

Table 32 Content: Information and Support

	Content: Information and Support
1	Ensure patients are actively involved in decisions about active surveillance e.g. repeat scans and re-biopsy
2	Encourage the inclusion of partner/family in education and consultations
3	Ensure patients understand prostate cancer
4	Ensure access or signposting to structured peer support locally
5	Ensure patients understand the risk of prostate cancer progressing
6	Ensure patients understand the other treatment options for prostate cancer
7	Provide access to up to date research on large active surveillance studies
8	Ensure patients understand the role of PSA/Gleason grade/Tumour volume in active surveillance

Table 33 Delivery of information

	Delivery of information
1	Offer face to face "information and support seminar" given to a group of men on active surveillance (hospital based)
2	Offer face to face 'information and support seminar' given to a group of men on active surveillance (at a local community centre)
3	Signpost to reliable online websites/webinars
4	Offer/Sign post (unbiased) to paper based information resources (from charities)
5	Where possible actively signpost patients to stories about public role models on active surveillance

7.4. Discussion

Following a systematic review of the literature, semi-structured interviews and subsequent review by an expert panel, our Delphi prioritisation method identified four themes defining

the priorities for successful supportive care: (1) principles of an active surveillance programme; (2) structure of consultations; (3) content: Information and Support; (4) delivery of information.

An increase in the number of men on active surveillance over the last 5 years (5), has led to an increasing interest in research themes based on active surveillance and survivorship/ 'living with' and beyond cancer, however, this concept is not new. NHS Improvement has been working as part of the National Cancer Survivorship Initiative (NCSI) to improve the quality and effectiveness of support for those living with and beyond cancer since 2011. The NCSI was set up as a recommendation arising from 'The Cancer Reform Strategy (2007) (294), with more recent reference to the work in the 'Improving Outcomes: a Strategy for Cancer' (20).

NHS Improvement has led the testing and development of stratified models of care and support that account for the needs of the patient in relation to the treatment received to achieve a more personalised approach to care with a greater degree of satisfaction (295).

This research has found that person-centred care can have a big impact on (296):

1) Improving the experience people have of care and help them feel more satisfied
2) People leading a healthier lifestyle, e.g. exercise or eating
3) People being more involved in decisions about their care to get the services and support that are appropriate for their needs
4) People's health outcomes, e.g. weight, fitness

The practice of person-centred care is predicated on supporting people to participate in their own care and recent government policy has therefore focused on emphasising and strengthening the voice of patients, moving away from a paternalistic model of care where professionals 'do things to/for' patients (297).

This model has been further endorsed by The Health Foundation (298), who work as an independent charity committed to better health and health care for people in the UK, using front line research and policy analysis, to inform effective policymaking. They propose a strategy for supporting self-management with the premise being that if people are educated about their condition and understand it, they are more inclined to feel confident about their treatment which ultimately increases adherence to their chosen treatment.

However, in order to practice personalised care in active surveillance, strong leadership, organisational and environmental support (299) is required to change current healthcare professional thinking and practices (as seen in our healthcare professional survey) to promote the need for active surveillance supportive care. This additional effort may present challenges within the current healthcare climate where the exigencies of everyday clinical practice are overwhelming. However, reducing the patients dependence on health care professionals by increasing their sense of control and wellbeing through education is a more intelligent, efficient and effective way of working', if our ultimate aim is to increase adherence to active surveillance.

7.5. Strengths and limitations

The benefits of this patient and public engagement project to identify priorities for active surveillance supportive care far outweigh its drawbacks. Traditionally, there has been a divide between quantitative and qualitative methods, however the Delphi method for research straddles this divide by virtue of its procedural structure (combining qualitative and quantitative phases), providing the opportunity to achieve a more complete picture of the phenomenon. A criticism of the Delphi method is low feedback rates due to the requirement for multiple rounds of answers which is integral to the concept of this process (82). In the case of poor response, the quality of information obtained could be discounted or at the least critically scrutinised, however, I did not experience this during this study. This may be in part be due to the recent availability and popularity of internet-based research tools (e.g. smart survey), meaning I was able to use the internet to mitigate Delphi's limitations, maximizing its advantages, and expanding the breadth of its application. The breadth of opinion, numbers of patients and healthcare professionals that engaged in this process as well as the speed of survey returns noted during this project confirms these findings. As a result only three participants failed to complete the second round of the survey.

Another criticism of the Delphi technique is its potential to mould opinion (300). This has been demonstrated in several studies which found that participants would rate their responses differently if feedback given between rounds was distorted (57, 75, 301). However, in this study the feedback given was interpreted by the expert Active Surveillance Reference Group, thereby mitigating any bias associated with single researcher

interpretation. Lastly, this study was based on local population (South West London), and thus the findings cannot be generalised.

7.6. Conclusion

Our findings have highlighted that a structured approach to active surveillance supportive care is desired by patients to increase active surveillance adherence.

It is imperative that patients, charities and Healthcare professionals collaborate to co-create supportive care interventions aimed at increasing adherence to AS, to ensure that the views of all key stakeholders involved in active surveillance are represented and any discordance is addressed through consensus.

8. Chapter VII – Conclusion and future directions

This PhD project was carried out in an area where little is known about the specific survivorship/supportive care needs of men on active surveillance for low to intermediate risk prostate cancer. The deliberate use of an applied research methodology was designed to inspire practitioners and future researchers to design interventions to increase long-term adherence to active surveillance, whilst ultimately decreasing the significant healthcare burden of over-treatment. The following chapter summarises the thesis and explores future research opportunities.

8.1. Summary of thesis

This thesis was inspired by an interest in prostate cancer active surveillance and supportive care (survivorship) that has influenced many of my recent career decisions.

Over the last five years there has been a significant improvement in cancer survival rates and professional and public pressure has resulted in government health policies (2013) (20), focussing on the needs of people living with or beyond a cancer diagnosis. However, to ensure that the current trend of over-treatment (302, 303) of indolent prostate cancer is halted, this still requires translation into practice in respect of active surveillance. Therefore, there is a need for qualitative health researchers to produce and present findings that are relevant to practice and for practitioners to interpret and evaluate their use in practice (86).

In the following section, I give a brief summary of each of the four stages of this project followed by proposals for future projects.

Stage 1 of this project was split into three parts that were carried out concurrently with the aim of exploring the rationale for the project and increasing my knowledge and awareness of the scientific literature.

Part I reviewed the impact of a local active surveillance intervention after five years of implementation. The intervention demonstrated a significant decrease in active surveillance drop-out over 5 years from 25% to 11% as the result of a single education seminar.

Part II was a systematic review of contemporary worldwide practice in active surveillance for low risk prostate cancer. This identified significant differences in practice guidelines across continents, countries and even hospitals.

Part III involved a mixed-methods systematic review to identify factors influencing both choice and adherence to AS. Six key themes were identified: (1) patient- and tumour factors (age, co-morbidities, knowledge, education, socioeconomic status, family history, grade, tumour volume, fear of progression/side-effects); (2) family and social support (awareness, acceptance, support); (3) provider (specialty, communication, attitudes); (4) healthcare organisation (geography, type of practice) and (5) health policy (guidelines, year, awareness).

Stage 2 of this project used semi-structured interviews to explore the barriers to active surveillance from the perspective of patients that had dropped out of active surveillance without evidence of cancer progression. This project identified five key themes; (1) experience of consultations (diagnosis and follow-up); (2) communication and shared decision making; (3) understanding of supportive and informational needs, psychological support, information, self-care; (4) administrative and organisational issues – waiting times, admin issues, local and national guidelines; (5) partner and peer support.

Stage 3 employed a process of meta-aggregation to combine both qualitative and quantitative data from the systematic review and the qualitative interviews into a table of items for inclusion in a 2-round modified Delphi technique to prioritise patient, public and healthcare professional priorities for active surveillance supportive care. Sixty-two items were developed into statements for consideration in the surveys. There was moderate agreement between patients and healthcare professionals on the priority items.

Stage 4 convened an expert patient and public involvement panel (The Active Surveillance Reference Group), to develop consensus statements based on the items prioritised in the two surveys. The agreed 24 statements were further categorised into four themes to give guidance on the key priorities for inclusion in active surveillance supportive care: principles of an active surveillance programme, structure of consultations, support and information and delivery of information.

In summary, this thesis provides insight into the supportive care needs of men on active surveillance for low to intermediate risk prostate cancer demonstrating how knowledge can be translated into national recommendations (NIHR Signal (304)) and local healthcare improvements for the benefit of men living with prostate cancer on active surveillance.

8.2. Future research direction

In order to take this work to the next level, I would like to propose the following as recommendations for future research:

1) The Delphi-method employed during this project was based on a local population. This could be replicated on a multisite basis (nationally or internationally) to define a universally agreed list of priorities for supportive care. This would prevent charities and other healthcare organisations from investing in interventions without the benefit of robust research supporting this premise.

2) Surveillance is not only an issue for men with prostate cancer. Hence, the research methodology and methods used could be replicated to explore T1a kidney cancer, where surveillance should be recommended, but is often disregarded in favour of radical treatment (305).

I have submitted a joint grant application (Kings College London, The Royal Free Hospital, The Royal Marsden Hospital and Frimley Park Hospital) to The Urology Foundation to progress the work on kidney cancer and have already successfully obtained a small kick-off grant of £10,000 from Kidney Cancer UK.

I look forward to using the skills that I have learnt over the last four years, by taking this research forward with respect to improving the lives of men with low-intermediate risk prostate cancer and T1a kidney cancer who are on active surveillance.

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10. Appendices

10.1. Appendix 1 European Urology Oncology paper (PDF)

EUROPEAN UROLOGY ONCOLOGY XXX (2018) XXX–XXX

available at www.sciencedirect.com
journal homepage: euoncology.europeanurology.com

European Association of Urology

A Single Educational Seminar Increases Confidence and Decreases Dropout from Active Surveillance by 5 Years After Diagnosis of Prostate Cancer

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Article info

Article history:
Accepted September 16, 2018

Associate Editor:
Gianluca Giannarini

Keywords:
Prostate cancer
Active surveillance
Intervention
Adherence

Abstract

Background: Researchers remain divided on the major causes of dropout from active surveillance (AS), with rates of up to 38% among men with no evidence of prostate cancer (PC) progression.

Objective: To develop and evaluate an educational intervention in terms of adherence to AS among men with low- to intermediate-risk PC.

Design, setting, and participants: We first carried out focus group discussions with men who had remained on and dropped out of AS to inform an intervention to increase adherence to AS. A total of 255 consecutive men who had selected AS were then recruited to either standard care (written information and access to a nurse specialist) or standard care and the intervention.

Intervention: An educational seminar was designed by patients and clinicians including information on imaging, biopsy techniques, understanding pathology, large AS cohorts - mortality and morbidity risk and diet and lifestyle advice.

Outcome measurements and statistical analysis: The proportion of men dropping out of AS for reasons other than disease progression was assessed at 1 and 5 yr after AS selection using multivariate logistic regression.

Results and limitations: Common themes influencing decision-making by men on AS were identified: (1) clinical consistency; (2) information; and (3) lifestyle advice. Addition of an educational seminar led to significantly fewer men dropping out of AS: at 1 and 5 yr the dropout rate was 25% and 42%, respectively, in the standard care group, compared to 11% and 22% ($p = 0.001$) in the intervention group. In the intervention group, 18 men failed to attend the seminar.

Conclusions: The AS dropout rate was halved following a single educational seminar delivered to groups of men with intermediate- or low-risk PC, even at 5 yr.

Patient summary: Men on active surveillance (AS) for prostate cancer feel more supported when provided with an educational seminar within 3 mo of their treatment choice. The seminar halved the number of men dropping-out of AS, even at 5 yr.

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https://doi.org/10.1016/j.euo.2018.09.007
2588-9311/

1. Introduction

According to European guidelines, a large proportion of men with localised low-risk prostate cancer (LRPC) do not require immediate treatment and can be monitored, an approach known as active surveillance (AS) [1]. However, international variation in determinants for safe AS inclusion and follow-up [2] continue to contribute to high AS dropout rates (up to 38%) among men with no evidence of disease progression [3].

Researchers remain divided on the major causes of AS dropout. A recent systematic review of AS choice and adherence literature [4] reported six domains driving unnecessary AS dropout: (1) patient characteristics; (2) tumour characteristics; (3) family and social support; (4) provider; (5) health care organisation; and (6) health policy.

However, studies have widely shown that informational interventions aimed at men on AS have a favourable impact on AS adherence. Oliffe et al. [5] found that self-management strategies helped men to cope with some of the long-term uncertainty of AS, while the Prostate Cancer Lifestyle trial, based on lifestyle modifications including exercise and attention to stress management, demonstrated an improvement in treatment-free survival on AS [6]. Goh et al. [7] found that men who perceived that they were receiving useful and consistent information were more satisfied with and therefore more likely to continue on AS, whilst the UK-based ProtecT trial [8] found merit in consistency of personnel to support and inform patients. Interventions relating to peer support have also yielded a significant improvement in the quality of life of men with any stage of PC [8,9].

Here we describe the development and evaluation of an intervention based on previous research efforts and local focus groups that uses a standardised information and support delivery technique with the aim of increasing AS adherence.

2. Patients and methods

This applied research project consisted of two parts: (1) focus groups (FGs) to understand the motivation and needs of men on AS and to explore practicalities of an intervention to support AS adherence; and (2) a pilot study to assess the intervention effect.

2.1. Focus groups

Permission was obtained from the local urology audit committee to identify potential participants through electronic records (permit no. U13887). In December 2009 and April 2010, two FGs were facilitated by the clinical nurse specialist (CNS) team. The first consisted of eight men who were currently on AS and the second of seven men who had dropped out of AS without evidence of PC progression. A semistructured question guide was developed to provide structure for each FG (Supplementary material) on the basis of a review of the available literature [10].

We used thematic analysis, an inductive process designed to identify and examine emerging themes from conceptual data [11]. Thematic saturation in qualitative data has been reported at 15 subjects in interview studies [12] and therefore two FGs were scheduled. Purposeful homogeneous sampling was used to provide conceptual significance to the question of adherence [13].

2.2. Developing the intervention

The intervention was developed in line with recommendations from the FGs. A Powerpoint presentation was coauthored by patients, nurses, and doctors, with final ratification by the AS reference group (4 partners of and 10 men currently or previously on AS).

The proposed 1.5-h seminar included information on: imaging; biopsy techniques; understanding pathology; the mortality and morbidity risks in large AS cohorts; and diet and lifestyle advice. Optimal seminar delivery was defined as a team approach between the urologist and CNS. Time was scheduled at the end of the seminar for questions and peer group discussion.

2.3. Recruitment

We used a consecutive sampling method [14] appropriate to a service improvement process in which a standard of care is evaluated before and after an intervention. The inclusion criteria were men diagnosed with low- to intermediate-risk PC (defined using the D'Amico classification system [15]; Supplementary Table 1) suitable for AS on the basis of information from magnetic resonance imaging (MRI) and transrectal prostate biopsy with confirmatory transperineal prostate biopsy. The AS progression criteria were: Gleason score 3 + 4 (transperineal biopsy approach, minimum of 24 cores) or where the maximum contiguous cancer length was $\geq$6 mm, MRI finding >T2b and $\geq$30% of cores positive. Follow-up was carried out according to National Institute for Health and Care Excellence (NICE) guidelines (Supplementary Table 2).

Between January 2011 and June 2011, 135 men were recruited (group A), and offered standard care [16] including introduction to a CNS and written information on AS [17]. A second consecutive group recruited between July 2011 and December 2011 (group B) included 120 men who were offered standard care and participation in the educational seminar.

We compared AS dropout rates at 1 and 5 yr after diagnosis. Patient and clinical characteristics at diagnosis and outcomes were compared between the groups using descriptive statistics. Multivariate logistic regression, after adjusting for age, grade, diagnostic prostate-specific antigen (PSA), digital rectal examination (DRE), and clinical stage, was used to assess whether differences in dropout rates were independent of patient characteristics.

3. Results

3.1. Qualitative analysis

3.1.1. Designing the intervention: FGs

The themes that emerged from the two FGs were: (1) consistency in the clinical team, administration, and follow-up protocol; (2) consistent information regarding PC and AS; and (3) diet and lifestyle advice.

3.1.1.1. Clinical consistency (panels 1 and 2). In both FGs, men described the importance of a consistent approach to follow-up as well as familiarity with the clinical team (Supplementary material).

Men still on AS found reassurance: "My CNS always sees me for my PSA review, I have a great relationship with her, I could ask her anything."

Men in the group that had dropped out of AS described their experience as stressful: "*Nobody could give me any guarantees about AS follow-up, every guideline seemed to be different. It made me very nervous.*" They also described inconsistencies in the clinical team as "*very difficult.*"

Please cite this article in press as: Kinsella N, et al. A Single Educational Seminar Increases Confidence and Decreases Dropout from Active Surveillance by 5 Years After Diagnosis of Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.09.007

3.1.1.2. Consistent information (panels 3 and 4). The two FGs differed in their response to the information given during AS. Those who had remained on AS felt that the amount of information given was adequate: "*I was given some information leaflets by my CNS. I thought they were very good.*" The men who had dropped out of AS described the information as inconsistent: "*Every time I saw a new doctor or nurse I would question them about PC and AS. Sometimes the answers were the same, other times they sounded like they didn't know what they were talking about.*"

3.1.1.3. Diet and lifestyle advice (panels 5 and 6). Men remaining on AS described self-help as a major contributor to their quality of life: "I found lots of information on the internet about diet and exercise. I changed my diet and began to go to the gym. I think everyone who has cancer should be aware. I've never felt better."

Men who had opted out of AS suggested that: "There really wasn't any information on how I might help myself on AS" and "I don't think the nurses or doctors believed that diet, exercise, or complimentary treatments would help on AS. I might have stayed on AS if I'd had the opportunity to discuss this."

3.1.2. Developing the intervention

The FGs discussed the medium through which the information and support should be given, including a website, bespoke written information, a webinar, and a peer-group seminar. Men who had dropped out of AS described their experience of websites and on-line forums as "*cold*". The men who had remained on AS felt that websites gave no opportunity for feedback and that forums, although interactive in some cases, were "*extreme and unpoliced.*" There was universal agreement that the content of the intervention should be empowering, with an emphasis on self-care. Of 15 participants, 13 agreed that a one-off peer-group educational seminar would suit the needs of the majority, with an option to reattend when/if required. It was suggested that the seminar should be held within 3 mo of choosing AS to mirror the early support and information that men undergoing radical treatment receive.

It was also suggested that the seminar content should be similar to our programme of seminars offered to men undergoing prostatectomy and radiotherapy [18]. Five topics were agreed on: imaging; biopsy techniques; pathology; mortality and morbidity risk in AS; and dietary and lifestyle advice.

3.2. Quantitative analysis

3.2.1. Patient demographics

A total of 273 men were recruited to the study. Eighteen men in the intervention group failed to attend the seminar and were therefore omitted from the final analysis. This left 255 men, 135 in group A and 120 in group B (Fig. 1).

There were no significant differences between the groups for age, PSA and DRE clinical stage at study entry (Table 1).

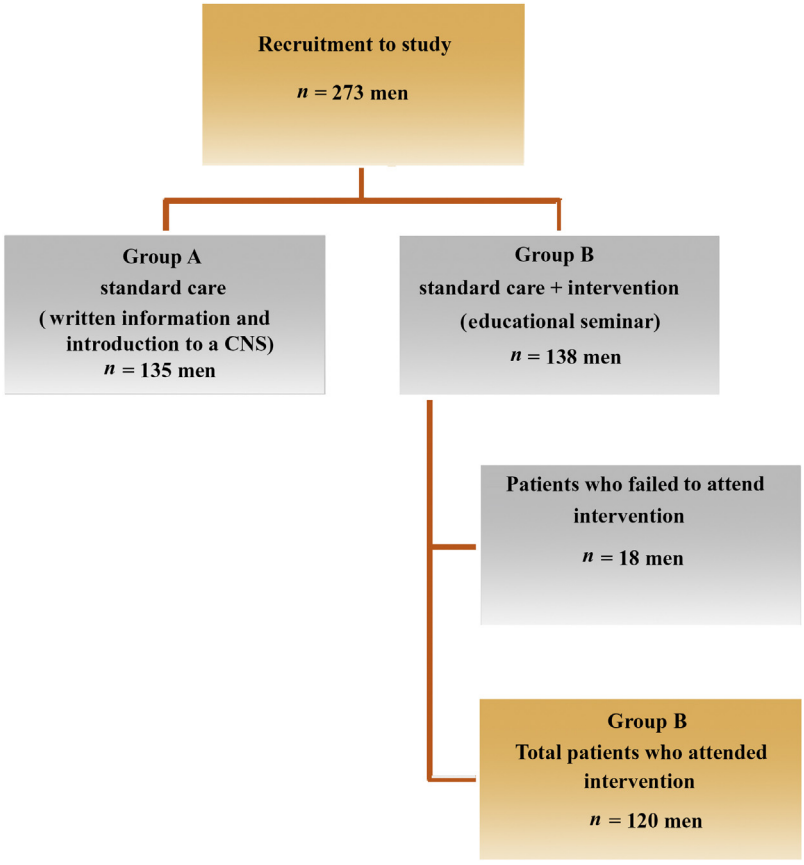

Fig. 1 – Intervention trial recruitment. CNS = clinical nurse specialist.

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Table 1 – Characteristics of participants in both arms of the nonrandomised intervention study

Characteristics at active surveillance entry	Standard care	Educational seminar	*p* value
Patients (*n*)	135	120	
Mean age, yr (standard deviation)	62.4 (6.8)	63.3 (7.4)	0.34
Mean prostate-specific antigen, ng/ml (standard deviation)	9.2 (7.0)	8.6 (5.3)	0.42
Gleason score, *n* (%)			
3 + 3	42 (31.1)	111 (92.5)	0.001
3 + 4	93 (68.9)	9 (7.5)	
Digital rectal examination assessment, *n* (%)			
Benign	47 (34.8)	46 (38.3)	0.56
T2	77 (57.0)	68 (56.7)	
T3	11 (8.2)	6 (5.0)	

However, there was a significant difference in Gleason grade group (GGG): 42 men (31%) in group A and 111 (93%) in group B had GGG1, while 93 (69%) in group A and nine (7%) in group B had GGG2. It was felt that this was most likely associated with an increase in confidence for local AS monitoring practice in the intermediate-risk PC group [19].

3.2.2. *Adherence to AS*

No man experienced clinical disease progression in the first year. However, 25% in group A and 11% in group B dropped out of AS ($p = 0.003$; Table 2).

By year 5, patients in group B remained less likely to drop out of AS. The dropout rate without evidence of progression was 21.7% in group B and 41.5% in group A ($p < 0.001$) (Table 2). Owing to the difference in clinical characteristics between the groups, the AS dropout rate due to cancer progression at 5 yr after diagnosis was higher in group B than in group A (21.7% vs 12.6%) [20,21].

The dropout rate remained significantly lower among seminar participants after adjustment for baseline clinical characteristics, including GGG, at both 1 yr (odds ratio [OR] 0.21, 95% confidence interval [CI] 0.09–0.49) and 5 yr (OR 0.26, 95% CI 0.12–0.56; Table 3). Identical results were found when restricting the analysis to GGG1, with an OR of 0.25 (95% CI 0.11–0.53) for dropout among patients without evidence of disease progression at 5 yr.

4. Discussion

This is the first mixed-methods study to develop an educational supportive intervention and assess its impact on AS adherence over a 5-yr period. Our findings demonstrate the effectiveness of a structured, interactive, educational seminar in increasing adherence to AS for men with low- to intermediate-risk PC.

The needs of men requiring radical treatments for PC have previously been examined and have helped to define and develop the role of the CNS in supporting patients [22]. However, less is known about the resources required by men selecting AS or engaging in long-term AS. A recent qualitative study suggested six requirements of men on AS [23]: (1) general information on PC and how to interpret results; (2) specific information on AS investigations, follow-up, and mortality risk; (3) complementary options regarding diet, lifestyle, and exercise; (4) a variety of resources; (5) social support and interaction; and (6) verification of the integrity of information. These requirements were reflected in our own FGs. Men who had opted out of AS felt particularly strong about this.

4.1. *The clinical team*

The patient relationship with the clinical team is an important variable in adherence to healthcare, but it is difficult to assess the nature of this interaction and to measure its components. Poor communication is traditionally measured in terms of a patients' inability to recall clinician instructions, with patients failing to recall between one-third and one-half of statements given to them [24]. One FG participant suggested:

> *"The doctor didn't even let me sit down, he greeted me at the door and said, 'Your PSA is fine, see you next year.' I had questions, I wasn't encouraged to ask them" . . . "after leaving the clinic I couldn't even remember what my PSA level was, I had to call the nurse later that same day. I was*

Table 2 – Active surveillance outcomes by intervention group at 1 and 5 yr

Program outcomes	Patients, *n* (%)		*p* value
	Standard care	Educational seminar	
At 1 yr			
Remained in the active surveillance program	101 (74.8)	107 (89.2)	
Dropped out due to disease progression	0	0	
Dropped out with no disease progression	34 (25.2)	13 (11.2)	0.003
At 5 yr			
Remained in the active surveillance program	62 (45.9)	68 (56.7)	
Dropped out due to disease progression	17 (12.6)	26 (21.7)	0.053
Dropped out with no disease progression	56 (41.5)	26 (21.7)	<0.001

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Table 3 – Multivariate logistic regression for the odds of dropout for reasons other than disease progression [a]

Parameter	Odds ratio (95% confidence interval)			
	At 1 yr	By 5 yr		
	(*n* = 253)	Whole cohort (*n* = 253)	Excl. men with DP (*n* = 210)	Excl. men with DP and GGG2 (*n* = 125)
Seminar intervention				
No	1.00	1.00	1.00	
Yes	0.21 (0.09–0.49)	0.25 (0.12–0.51)	0.26 (0.12–0.56)	0.25 (0.11–0.57)
Age (continuous)	1.03 (0.98–1.09)	0.94 (0.91–0.98)	0.93 (0.90–0.98)	0.95 (0.90–1.00)
PSA (continuous)	0.94 (0.88–1.01)	0.96 (0.52–1.01)	0.98 (0.93–1.04)	0.97 (0.89–1.06)
GGG				
GGG1	1.00	1.00	1.00	–
GGG2	0.44 (0.20–0.97)	0.49 (0.23–1.00)	0.48 (0.22–1.02)	–
DRE				
Benign	1.0	1.00	1.00	
T2	0.88 (0.43–1.79)	0.98 (0.54–1.77)	0.93 (0.50–1.72)	0.75 (0.33–1.71)
T3	1.42 (0.41–4.91)	1.69 (0.54–5.32)	3.88 (0.96–15.7)	3.52 (0.51–24.0)

Excl. = excluding; DP = disease progression; GGG = Gleason grade group; PSA = prostate-specific antigen; DRE = digital rectal examination.
[a] All models were adjusted for age, grade, diagnostic PSA, DRE, and clinical stage.

told all I needed to know was that I didn't need to worry myself—that was it, end of conversation".
[Participant 9, 69 yr]

Initial selection of AS is strongly associated with multidisciplinary care [25]. However, while multidisciplinary clinics are recognised as advantages in optimising AS choice, our FG feedback suggests that variability in personnel managing AS leads to specific concerns regarding consistency. This was demonstrated through commentaries from several participants (panel 2; Supplementary material).

However, it has been found that a combination of a CNS and a doctor benefited men with PC. Tarrant et al. [26] and Ream et al. [27] found that men who had accessed a CNS reported a more positive experience of their cancer management. Our FGs confirmed that a combination of medical and nursing staff was optimal in giving information and supporting men on AS (panel 1; Supplementary material).

4.2. Detailed and consistent information

Information has a variety of benefits for cancer patients, particularly in reducing anxiety, improving the ability to cope with treatment, and in achieving better self-care. Information can help to empower patients. Recognition of the role that support and information play in effective cancer care is not new. In 2002, NICE commissioned a report on improving outcomes in urological cancers [28]. It recognised that in PC in particular, the appropriate management strategy may depend on an individual's values and attitudes, but should include: information about basic anatomy and pathology; PC and individual variation in its impact and rate of progression; treatment options; probability of survival; symptom reduction; risks; and potential short- and long-term effects. Our FGs reported frustration in this respect, describing a lack of clarity about the information provided that appeared to extend to the medical and nursing team (panel 4; Supplementary material).

O'Callaghan et al. [29], Oliffe et al. [5], and Davison and Breckon [30] found that patients on AS became particularly stressed when information given by the clinical team was contradictory or inconsistent. Our FG participants also agreed that there was inconsistency, describing a lack of objective and robust information, and poor descriptors of disease risk and AS (panel 4; Supplementary material).

The FGs discussed both the delivery method and the type of information and support required. All agreed with a 2010 FG study that reported that information on the internet was contradictory, limited, and difficult to find [31] and therefore a dedicated informational source was required.

Many of the men who had dropped out of AS and later chose to undergo radical treatment also remarked on the inconsistent approach to information and support services between men offered AS and those undergoing radical treatment.

Our group previously reported a significant increase in patient satisfaction when men were offered access to a peer-group educational seminar on radical prostatectomy [18]. Galbraith et al. [32] described how this can provide a sense of meaning in men's experience of PC. FG participants also suggested that mimicking the information and support given to patients in other treatment groups might influence the behaviour of the health professional team by endorsing AS as a valid treatment option [4].

4.3. Diet and lifestyle advice

A 2015 systematic review of supportive care in PC highlighted self-care in nine papers [33]. The authors discussed the empowerment and sense of control that come from self-care through lifestyle changes. Nanton et al. [34] found that by "taking an active part in their own health

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management, men were taking control of their illness." This was also described by Oliffe et al. [5] and O'Shaughnessy et al. [35], who demonstrated the merits of using strategies similar to those for men at other stages of disease combining "living a normal life" with "doing something extra", such as dietary or lifestyle changes. This appeared to increase both acceptability and adherence to AS and was also described by our FG participants (panel 5; Supplementary material).

4.4. Study limitations

Our assignment of men to intervention and standard care was not randomised, but occurred over consecutive time periods as part of an audit/service improvement project in which the intervention was the "new" standard of care. It is not possible to exclude the influence of clinical practice that may have occurred over this time period, such as initial undersampling because of the experience of the biopsy practitioner the learning curve of MRI team. This might have contributed in part to the higher proportion of men progressing in the intervention group despite a significantly higher number of men with GGG1 at diagnosis.

In addition, the two comparison groups differed in GGG, which might have influenced adherence. However, the differences remained statistically significant, even after adjustment for clinical characteristics such as GGG at diagnosis. However, we were unable to adjust for other recognised confounding factors such as marital status, ethnicity, and education level.

Eighteen patients were excluded from the study as they failed to attend the seminar intervention. Follow-up with this patient group might have added value in reducing future non-attendances.

5. Conclusions

Our study findings demonstrate that men on AS desire consistency for staff contact, appointments, and information. Subsequent evaluation of this intervention revealed that a peer-group educational seminar delivered by the clinical team in the initial months after starting AS reduced the likelihood of dropping out of AS by 50%. With the trend towards AS in LRPC increasing, interventions like this one could help in reducing the upward drift in health care costs worldwide.

Author contributions: Netty Kinsella had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kinsella, Cahill, Van Hemelrijck, Challacombe, Popert, Brown.
Acquisition of data: Kinsella, Cahill.
Analysis and interpretation of data: Kinsella, Van Hemelrijck, Beckmann.
Drafting of the manuscript: Kinsella, Beckmann.
Critical revision of the manuscript for important intellectual content: Brown, Cahill, Elhage, Cathcart, Challacombe, Popert, Van Hemelrijck.
Statistical analysis: Beckmann, Van Hemelrijck.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Brown, Cahill, Van Hemelrijck.
Other: None.

Financial disclosures: Netty Kinsella certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.euo.2018.09.007.

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Please cite this article in press as: Kinsella N, et al. A Single Educational Seminar Increases Confidence and Decreases Dropout from Active Surveillance by 5 Years After Diagnosis of Prostate Cancer. Eur Urol Oncol (2018), https://doi.org/10.1016/j.euo.2018.09.007

10.2. Appendix 2 Table D'Amico Risk stratification for clinically localised PC

Risk group	Criteria
Low risk	PSA <10ng/ml and highest GGG ≤ 6 and clinical stage T1c or T2a
Intermediate risk	PSA ≥ 10 but $\leq 20ng/ml$ or highest GGG =7 Or clinical stage T2b
High Risk	PSA $\geq 20ng/ml$ or highest GGG ≥ 8 or clinical stage T2c/T3

10.3. Appendix 3 Focus group discussion guide

Focus group 1: Men who had opted out of AS

1. Please share your experience of AS – any concerns or positive experiences
2. What information sources did you access whilst making the decision to select AS and during your time on AS?
3. Did you find any inconsistency in information sources?
4. What information would have been most useful whilst on AS?
5. What support services have you used and what is your experience of them?
6. Did you get adequate support from your clinical team (doctors and nurses) whilst on AS?
7. What support services would you have liked at this time?
8. Do you or have you ever accessed a support group either face to face or online whilst on AS? If so how useful was this?
9. Where did you get most of your information from e.g. clinical team, online, other sources?
10. Did you access information about diet and lifestyle advice whilst on AS?
11. What were your experiences of follow-up during your time on AS?
12. Were you aware of national or international guidelines on AS e.g. patient selection, monitoring and triggers for recommending treatment?
13. What was your motivation for opting out of AS?
14. What would have encouraged you to remain on AS?

Discussion guide - Focus group 2: Men currently on AS

1. Please share your experience of AS – any concerns or positive experiences?
2. What is your motivation for remaining on AS?
3. What information sources did you access whilst making the decision to select AS and during your time on AS?
4. Have you ever found inconsistency in information sources?
5. What information would be most useful whilst on AS?
6. What support services have you used and what is your experience of them?
7. Do you get adequate support from your clinical team (doctors and nurses)?
8. What support services would you ideally like?
9. Do you access a support group either face to face or online? If so how useful is this?
10. Where do you get most of your information from e.g clinical team, online, other?
11. Is information on diet and lifestyle important whilst on AS?
12. Have you changed your diet or exercise whilst on AS?
13. What has been your experience of follow-up on AS?
14. Are you aware of national or international guidelines on AS e.g. patient selection, monitoring and triggers for recommending treatment?

10.4. Appendix 4 Focus Group Panels

Panel 1: Focus group 1: Men on active surveillance

Consistent clinical team, administration and follow-up protocol

Participant	Age	Months on AS	Quote
1	65	29	"My nurse specialist always sees me for my PSA review, I have a great relationship with her, I could ask her anything. I trust that she is following the follow-up protocol as she is able to put my results into context and we discuss what will happen at the next visit every time I come".
2	71	43	" I found the leaflet on active surveillance really important. I needed to understand how often I would be seen and what I could expect in terms of tests. I'm really happy as I usually see the same 2 or 3 doctors or nurse – it adds to a feeling of consistency.
3	64	28	"Being in a dedicated active surveillance clinic – I'm not? Oh, I thought I was, I always see the same person".
4	70	54	"An explanation of the next steps of follow-up every time I go to clinic is really important - reassuring".
5	66	43	"I have had a couple of appointments moved but this is understandable over a 4 year period".
6	58	40	"When my appointments are moved I can always contact my nurse specialist, he's always very helpful and has sometimes given me my results over the phone to save me a trip to hospital".
7	69	33	"Access to my nurse specialist is most important to me"
8	51	31	"Always being able to leave a message and someone getting back to me".
8	51	31	"I can often get my results over the phone which is much more convenient".
6	58	40	"There are some questions I need to ask a doctor. Some reassurances are needed from a doctor but some things I need to speak to my nurse about".
3	64	28	"'I get more time from my CNS, most of the time I just need encouragement to stay with the programme"
5	66	43	"My nurse is great, she checks up on me. I wouldn't have committed to my new diet and exercise plan if she hadn't. It felt like she was invested in me, that what I was doing was really helping me control my cancer".

Panel 2: Focus Group 2: Men who had opted out of active surveillance

Consistent clinical team, administration and follow-up protocol

Participant	Age	Months on AS	Quote
9	69	12	'The doctor didn't even let me sit down, he greeted me at the door and said your PSA is fine, see you next year. I had questions, I wasn't encouraged to ask them'…..'after leaving the clinic I couldn't even remember what my PSA level was, I had to call the nurse later that same day. 'I was told all I needed to know was that I didn't need to worry myself – that was it, end of conversation'.
10	66	19	'I saw another new doctor. She kept looking for a piece of paper that she explained was the follow-up protocol. She changed her mind 3 times before I had the correct information. I might have missed an important scan if I hadn't asked additional questions. My confidence was gone, I was upset. She apologised and said it was her first week with a new team. Not being funny, but that wasn't my problem'
11	64	24	'I'd never met the oncologist before. I just felt like they were changing the goal posts, I was comfortable with the urology team seeing me every 6 months then the oncologist suggested 3 monthly blood tests. There was just no consistent plan'
12	55	12	"I don't think people appreciate that when your appointment is approaching you feel anxious and stressed. When they cancelled my appointments I started to question just how safe it really was. I couldn't cope with that". And, "My nurse didn't think changing my appointments was a big deal, she just kept saying that I was one of the lucky ones and that I didn't need to worry – easier said than done!".
13	63	18	"I work away - there should be a direct line to the admin team, I always went round the houses when I needed to change an appointment"
14	59	18	"appointments shouldn't be cancelled unless you speak to the patient. I got several letters in the post and worried myself sick whenever an appointment was brought forward. I thought it was because of my cancer, I

			didn't realize it was because of someone's' holiday. At the very least this should be explained at the beginning".
15	70	12	"I never felt like I was seeing a specialist in AS. I just wanted someone to be interested in AS".
11	64	24	"Nobody could give me any guarantees about AS follow-ups, every guideline seemed to be different. It made me very nervous".
14	59	18	"Very difficult. I didn't feel that I had a relationship with anyone as I didn't see the same person more than twice" and…. "when I saw someone new, which was every other time I came to clinic, it was like starting again".

Panel 3: Focus Group 1: Men on active surveillance

Detailed and consistent information

Participant	Age	Months on active surveillance	Quote
6	58	40	"I know that a friend of mine went to a class before he had his prostate out, they should do that for men on AS"
7	69	33	"The PCUK website is updated all the time, it was a great recommendation for information"
1	65	29	"I like asking questions when I see my team. I think that's the only way you keep up to date"
7	69	33	"I go to the support group once a month, it means I can speak to a nurse every month if I need to"
5	66	43	"I go to the support group as well, I think the expert education sessions that they run are brilliant".
3	64	28	"I was given some information leaflets by my CNS. I thought they were very good"
4	70	54	"I asked lots of questions about PC when I was first diagnosed, I trusted that the doctor was giving me the right information. I was given some leaflets which I think I read, but I haven't re-read them since. I think it's more important to ask questions at each appointment".

Panel 4: Focus Group 2: Men who had opted out of AS active surveillance Detailed and consistent information

Participant	Age	Months on active surveillance	Quote
9	69	12	"You can't just tell someone not to worry about 'Cancer". If I had better understood how slowly my cancer was growing I might have stayed on AS. The doctor used words like you "could" stay on AS and its "possible" you won't need treatment. Believe me, when you've got cancer you need more reassurance!"
10	66	19	"I asked for some websites that I could look at.. When I had looked through them I drifted onto others that were frightening. I spoke to my CNS who just kept telling me not to worry. It would have been nice to have sat down with the doctor to answer some time of the questions I had. I got the sense that my cancer was insignificant and therefore so was I"
12	55	12	"Every time I saw a new doctor or nurse I would question them about PC and AS. Sometimes the answers were the same, other times they sounded like they didn't know what they were talking about. They weren't able to answer questions about my situation in relation to the average AS patients. It didn't fill me with confidence"
14	59	18	"The only time the doctor seemed keen to discuss my cancer was when I said I wasn't happy to continue AS. I spent an hour with him then but up until that point appointments had been rushed - I felt like I was annoying them for asking too many questions".
12	55	12	"It's difficult to be told you've got cancer at 49 and told you don't need treatment but someone would see me every 3 months. If they had to check on me that frequently that didn't seem very safe to me. I wasn't offered any context"

15	70	12	"I think there should be a dedicated clinic for men on AS. Every time I saw a new doctor they changed the follow-up – why couldn't we have a copy of the AS follow-up guideline".
14	59	18	"I opted out of AS as I didn't feel like I was getting a straight answer. I kept asking when would I know that I needed treatment and I got a different answer each time'…..'I now know that it's different for everyone depending on prostate size and grade and number or biopsy cores, but nobody explained that at the time"
11	64	24	"I was given some information on AS, I think it was 2 pages long, I spoke to my friend who had also been told he had PC, he was given 4 booklets, when I asked my nurse why that was she said I was lucky, that I didn't need to worry about my type of cancer – I didn't know what this meant, but she didn't offer any more information"
14	59	18	"I'd had very little information or support whilst I was on AS. When I decided I would have surgery suddenly I was attending a seminar, was encouraged to attend the support group and was in regular contact with my nurse – for the first time I felt in control of my cancer, and most importantly not alone".

Panel 5: Focus Group 1: Men on AS

Diet and lifestyle advice

Participant	Age	Months on active surveillance	Quote
7	69	33	"I changed my diet and started to swim twice a week, and finally felt as if I was doing something positive, something that would help me"
4	70	54	"The most useful conversation I had with my doctor and nurse was about diet and lifestyle changes, I know there wasn't much evidence for it but it's made a huge difference to me. I've lost 3 stone and I've been able to stop my blood pressure tablets. It sounds strange but this cancer has given me back my life, I'm fit and healthy and able to keep up with the grandkids!"
2	71	43	"I've joined a cancer and complimentary therapies group on the PCUK forum, it's really helped with advice"
3	64	28	"My doctor didn't know anything about diet or exercise, he suggested I speak to my specialist nurse – she didn't know anything useful either. Everything I did was researched on the internet. I don't know if it was all correct but at least I felt like I was involved and taking charge of my cancer!"
8	51	31	"I had a really good chat with my doctor when first diagnosed, I was really pleased that he seemed to know how important it was to feel that I was doing something proactive"
4	70	54	"My nurse had lots of advice on where to go for free exercise classes. I've joined a walking group and a local gym".
6	58	40	"I found lots of information on the internet about diet and exercise. I changed my diet and began to go to the gym. I think everyone who has cancer should be aware. It's kept my mind and body busy, I've never felt better"

8	51	31	“My nurse specialist didn’t seem to know much about these things but suggested a great website so that I could investigate myself. I’ve now been on a couple of courses – it’s really been empowering”.
2	71	43	“I must have had the same CNS. Mine suggested a website too and I’ve been on a couple of courses in Bristol – it’s been a really positive experience”.

Panel 6: Focus Group 2: Men who had opted out of AS

Diet and lifestyle advice

Participant	Age	Months on AS	Quote
14	59	18	“There really wasn’t any information on how I might help myself on AS” and “I don’t think the nurses or doctors believed that diet, exercise or complimentary treatments would help on AS. I had done lots of reading and I couldn’t engage them in this so I gave up. I might have stayed on AS if I’d had the opportunity to discuss this”
9	69	12	“I didn’t know this was important, had I known I might not have stopped AS. I just felt helpless and I needed some control”
11	64	24	“I think we should have been offered some education on this stuff. I might have felt more positive if I had been”.
12	55	12	“Any information on these things would have been good. I felt like an idiot when I mentioned these at my first appointment. The nurse was very dismissive”.

10.5. Appendix 5 TAU paper

Review Article

Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices

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Abstract: In the last decade, active surveillance (AS) has emerged as an acceptable choice for low-risk prostate cancer (PC), however there is discordance amongst large AS cohort studies with respect to entry and monitoring protocols. We systematically reviewed worldwide AS practices in studies reporting ≥5 years follow-up. We searched PubMed and Medline 2000-now and identified 13 AS cohorts. Three key areas were identified: (I) patient selection; (II) monitoring protocols; (III) triggers for intervention—(I) all studies defined clinically localised PC diagnosis as T2b disease or less and most agreed on prostate-specific antigen (PSA) threshold (<10 µg/L) and Gleason score threshold (3+3). Inconsistency was most notable regarding pathologic factors (e.g., number of positive cores); (II) all agreed on PSA surveillance as crucial for monitoring, and most agreed that confirmatory biopsy was required within 12 months of initiation. No consensus was reached on optimal timing of digital rectal examination (DRE), general health assessment or re-biopsy strategies thereafter; (III) there was no universal agreement for intervention triggers, although Gleason score, number or percentage of positive cancer cores, maximum cancer length (MCL) and PSA doubling time were used by several studies. Some also used imaging or re-biopsy. Despite consistent high progression-free/cancer-free survival and conversion-to-treatment rates, heterogeneity exists amongst these large AS cohorts. Combining existing evidence and gathering more long-term evidence [e.g., the Movember's Global AS database or additional information on use of magnetic resonance imaging (MRI)] is needed to derive a broadly supported guideline to reduce variation in clinical practice.

Keywords: Active surveillance (AS); cohort study; prostate cancer (PC)

Submitted Dec 11, 2017. Accepted for publication Dec 18, 2017.
doi: 10.21037/tau.2017.12.24
View this article at: http://dx.doi.org/10.21037/tau.2017.12.24

Introduction

Prostate cancer (PC) is the second most common cancer diagnosis and the fifth leading cause of cancer mortality in men (1). In 2012, 1.09 million men were diagnosed worldwide, thus representing a substantial public health burden. The use of prostate specific antigen (PSA) testing and improvements in diagnostic procedures such as imaging and ultrasound guided biopsy have led to a significant increase in early diagnosis of localized, low-risk PC (LRPC), ranging from 10–80% of all men diagnosed with PC worldwide (1), and a subsequent decrease in PC mortality (2-4).

A substantial proportion of men with LRPC do not need treatment with surgery or radiation, but can be carefully monitored—an approach known as active surveillance (AS). Overtreatment of LRPC is of concern, not only because of the physical and psychological morbidity associated with radical treatment, but also because of the economic healthcare burden (5,6). AS is considered a safe alternative to immediate treatment and is endorsed by national medical organizations and guideline groups as a viable management option for men with LRPC (7).

More specifically, AS for LRPC can be defined as a treatment strategy of close monitoring through blood tests (PSA), digital rectal examination (DRE), imaging and prostate biopsy, with conversion to curative treatment if progression occurs (8,9). Large cohort studies have shown that with appropriate patient selection, risk of dying from PC in men on AS is low: 0.1% to 5.7% over 10–15 years (*Table 1*). However, inconsistency in selection and adherence to AS remains. Studies suggest that patient preference (23,24), physician (25,26), family and peer group influence (27,28), National guidelines (29,30) and local practices (31,32) all influence this process. There is also no doubt that anxiety surrounding disease progression also plays a significant role (33-35) in influencing long-term AS adherence. It is reported that cancer continues to cause more fear than debt, knife crime, Alzheimer's disease and unemployment (36). Unsurprisingly therefore, studies continue to report that 1.6% to 38% of men opt out of AS often with no or little evidence of disease progression within 5 years (*Table 1*).

However, in the last 10 years a trend towards AS adoption in LRPC has been reported by many large database studies, with some variation still noted between countries, practices and physicians (37). Most notable are the upward trends seen in North America, Australia and Europe. In 2015, Cooperberg and Carroll reviewed US trends in AS reporting from the US CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) database. This demonstrated a sharp rise in the uptake of AS, from 10% over the past 20 years to 40% in 2010–2013 (4). This was replicated in Europe with the Swedish National PC Register reporting a rise from 40% to 74% between 2009 and 2014 (30) and in Australia, where the Victorian PC Registry (38) reported a 16% rise in AS uptake between the first half of 2010 and second half (23.9% to 39.7%). This level (39%) was maintained over the following 2 years further increasing in 2015 up to 42.8% (39). This was also demonstrated in hospitals reporting on radical prostatectomy in both Canada and Germany. In Canada (Toronto), Louis and authors (40) reported a steady decline in the number of radical prostatectomies carried out for LRPC from 2007 (40.6%) to 2012 (13.6%), whilst in Germany the Martini Clinic (41) demonstrated a similar decrease for low-risk Gleason score 6 cancer in 2014 (12.1%) in comparison to 52.2% in 2000.

However, this increase is not universal. In contrast, a 2014 survey (42) of 2,133 Japanese urologists suggested that 26.9% reported no use of AS for LRPC and another 50.6% reported using AS in <5% of their patients. Moreover, only 27% of respondents indicated that they would want to offer AS more frequently in the future.

The increased use of AS seen in some countries suggests that the global trend towards conservative management for LRPC is gathering pace, however the fact that there is no worldwide consensus on defining favourable risk disease (43) in AS suggests that there is still some way to go in gaining universal acceptance.

This review aims to evaluate the literature describing contemporary AS practices worldwide and explores the importance of Movember's GAP3 (Global Action Plan Prostate Cancer—Active Surveillance) collaborative effort in answering the key questions: what defines safe patient selection? What should the surveillance strategy look like? What clinical triggers are important in recommending radical treatment?

Search strategy

Studies documenting AS cohorts with a minimum of 5 years' follow-up published before October 2017 were identified through a systematic search of electronic databases (PubMed/Medline 2000-now and Embase) using the following key search terms: "prostate cancer", "active surveillance", "follow-up", "cohort", and their relevant

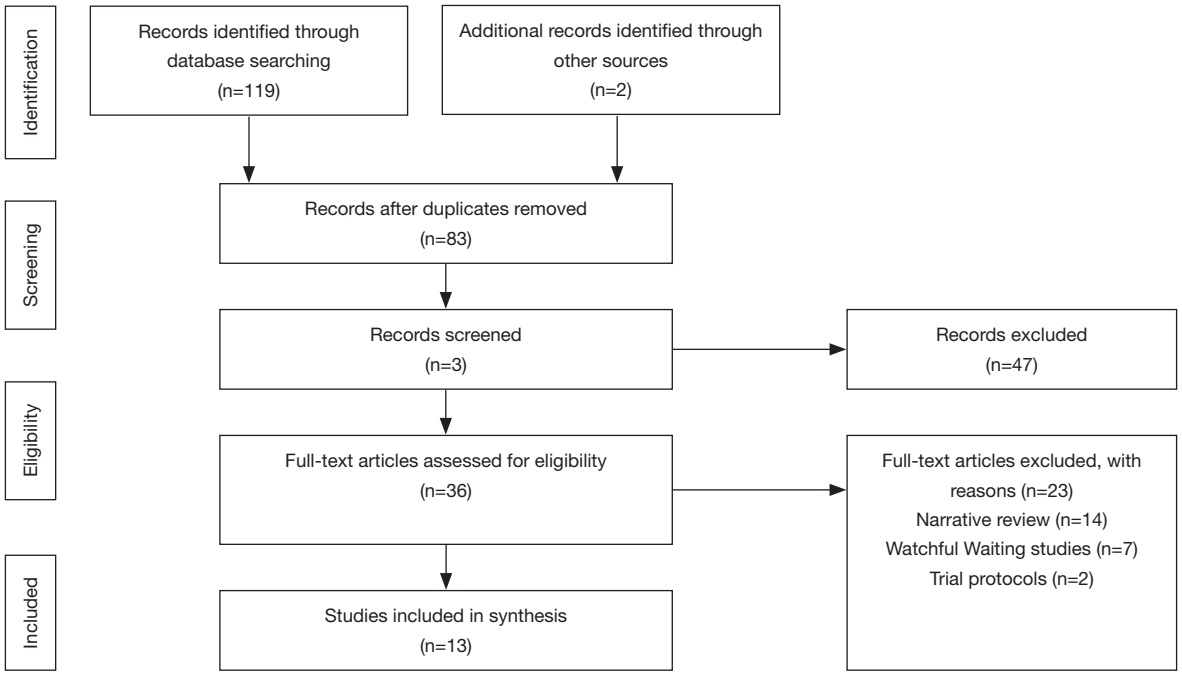

Figure 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram.

synonyms. Cited references were searched and retrieved for potentially eligible publications.

Studies of primary interest were those describing baseline and clinical characteristics of the study population, patient selection criteria, monitoring/surveillance protocol, AS drop-out, triggers for conversion to radical treatment and outcomes during follow-up (5-year studies with a median follow-up >18 months).

Findings

We identified 119 unique citations; of these 83 were excluded as review articles, commentaries, narratives, abstracts or where median follow-up was less than 18 months. Full-text screening was carried out on 36 articles, of which 23 were excluded, rendering 13 articles included (*Figure 1*—PRISMA diagram) each describing a unique AS cohort. Of the 13 included cohort studies (10-22), 6 took place in North America (10-12,14,17,21), 5 in Europe (15,16,18,20,22), 1 worldwide (13) and 1 in Australia (19).

The general demographic and follow-up characteristics of the published AS cohorts in this review vary considerably (*Table 1*). The average age across the studies was 65 years old. The number of participants studied ranged from 238 to 2,494 men. The number of months' follow-up ranged from 19 to 180 months.

The main findings in terms of AS adoption/patient selection, monitoring protocols and trigger points for intervention or re-assessment across the different AS studies are described below.

AS patient selection

Thirteen international AS programmes met our inclusion criteria, describing guidelines for AS patient selection (*Table 2*). These are described with respect to selection criteria based on the following components: (Tumour Nodes Metastases) TNM stage, PSA level, PSA density, percentage of cancer in prostate cores, number of positive cores and Gleason grading.

TNM stage

All cohorts agreed eligibility for AS meant clinically localised PC, with half of the cohorts using T2a or less, two [John Hopkins (11) and Goteborg (20)] opting to follow the Epstein criteria of T1c (in at least one arm of their cohort study). At the other end of the spectrum, three studies also included patients with T2b [(St Vincent's, Australia (19), Canary PASS (21) and Milan (22)] and two cohorts men diagnosed

Table 1 Overview of large cohort active surveillance studies

Study	Study period	Country	Patient No.	Median age (years)	Median PSA (ng/mL)	Follow up (median)	Prostate cancer specific survival (progression free survival)	Conversion to treatment	Conversion without evidence of clinical progression
MSKCC, 2011 (10)	Sept 1997–Feb 2009	USA	238	64	4.1	1.8 years (in patients without clinical progression); 11% of patients were followed at least 5 years without progression	2- and 5-year progression-free probability 80% and 60% respectively	Not reported	Not reported
John Hopkins, 2015 (11)	Jan 1995–June 2014	USA	1,298	66	4.8	5 years (VLRPC), 3 years (LRPC)	99.9% (VLRPC), 99.4% (LRPC) at 10 years; 99.9% (VLRPC), 99.4% (LRPC) at 15 years	50% at 10 years; 57% at 15 years	17%
UCSF, 2015 (12)	1990–2013	USA	810	62	5.3	5 years	98% at 5 years (40%)	40% at 5 years	Not recorded
PRIAS, 2013 (13)	Dec 2006–May 2012	Worldwide (17 countries)	2,494	66	5.6	1.6–3.1 years	100% at 4 years	34% at 4 years	9% (further 17.6%–solitary PSA increase, urinary symptoms or patient preference)
University of Miami, 2010 (14)	Feb 1992–2009	USA	230	64	4.8	32 months	100% at 44 months	14% at 44 months	Not recorded
Royal Marsden, 2013 (15)	March 2002–May 2011	UK	471	66	6.4	5.7 years	96% at 5 years	31% at 5 years	Not recorded
ProtecT, 2016 (16)	1999–2009	UK	545	62	Not recorded	10 years	99.4% at 5 years; 98.8% at 10 years	54.8% at 15 years	38% at 15 years
University of Toronto, 2015 (17)	1995–May 2013	Canada	993	68	Not recorded	6.4 years	98.1% at 10 years; 94.3% at 15 years	25% at 5 years; 45% at 15 and 20 years	1.6% (±2% not reported)
University of Copenhagen, 2015 (18)	2002–2013	Denmark	317	65	6.6	5 years	Unknown	39.5% at 5 years	Not recorded
St Vincents, 2015 (19)	1998–2012	Australia	796	63	6.2	67 months	100% at 67 months	38% at 67 months	12%

Table 1 (*continued*)

Table 1 (*continued*)

Study	Study period	Country	Patient No.	Median age (years)	Median PSA (ng/mL)	Follow up (median)	Prostate cancer specific survival (progression free survival)	Conversion to treatment	Conversion without evidence of clinical progression
Goteborg, 2016 (20)	Jan 1995–Dec 2014	Sweden	439	65	Not recorded	6 years	100% (VLRPC) at 10 and 15 years; 100% and 94% (LRPC) at 10 and 15 years; 98% and 90% (IRPC) at 10 and 15 years	53% at 10 years; 66% at 15 years	10% (further 8% urinary symptoms or unknown)
Canary PASS, 2016 (21)	2008–2013	USA	905	Not available	Not recorded	(8.4 months)	100% at 28 months	19% at 28 months	32%
Milan (SAINT + PRIAS), 2017 (22)	2005–2007 (SAINT); 2007–2016	Italy	818	66	5.7	11 years	100%	50% at 5 years	32%

with T2c disease [Canary PASS (21) and Milan (22)].

PSA level

Agreement between ten of thirteen cohorts suggested a PSA cut-off of 10 µg/L, the University of Toronto (17) and Royal Marsden (15) suggested an upper limit of 15–20 µg/L depending on life expectancy and age (>65 years) respectively. Only Goteborg (20) and Canary PASS (21) suggested an acceptable PSA for intermediate-risk disease of <20 µg/L.

PSA density

PSA density was featured in five cohorts (11,13,20-22). However, there was no consensus, with Milan (22) and PRIAS (13) suggesting a cut off of 0.2 and John Hopkins (11), Goteborg (20) and Canary PASS (21) opting for a more conservative 0.15.

Gleason grading

All included cohorts defined entry into AS as men with low-risk disease—Gleason 3+3 or less. The Canary PASS (21) and Goteborg cohorts (20) defined an entry criteria for men with intermediate-risk disease as Gleason 3+4, whereas The Royal Marsden (15) suggested men over the age of 65 were acceptable for entry into AS with Gleason 3+4.

Number of positive cancer cores

There was more agreement between institutions on the number of positive cancer cores (11 cohorts), which ranged between 2 and 3 cores in most cases. University of California San Francisco (UCSF) (12) suggested the number of cores should not exceed 33% of the total number of cores taken and the St. Vincent's Australia (19) cohort criteria suggested 20% as a reasonable cut-off.

Percentage of cancer in prostate core

Five of thirteen cohorts [Memorial Sloan Kettering Cancer Center (MSKCC) (10), Johns Hopkins (11), UCSF (12), Royal Marsden (15) and Milan (22)] agreed that no prostate core should contain more than 50% cancer with three cohorts [University of Miami (14), St Vincent's Australia (19) and Canary PASS (21)] suggesting a more conservative 20–34% (14,19). Five cohorts made no mention of percentage of PC in cores and therefore it is assumed this was not part of their selection criteria.

Monitoring protocols (Table 3)

Following initiation of an AS programme, most guidelines

Table 2 Criteria for entry into active surveillance programme

Study	Maximum T score/age/life expectancy	PSA (µg/L)	PSA density ng/mL (PSAD)	Gleason score	Minimum number of cores taken pre-AS selection	Maximum No. of positive biopsy cores (% of total cores)	Additional confirmatory re-biopsy	MCL (percentage of biopsy core positive)	Imaging
MSKCC (10)	T2a	<10	None recorded	3+3	10	3	Yes	(50%)	No
John Hopkins (11)	T1c (VLRPC)	None recorded	<0.15	3+3	12	2	No	(50%)	No
	T2a (LRPC—older men only)	<10	Not recorded	3+3	12	2	No	(50%)	No
UCSF (12)	T2	<10	Not recorded	3+3	Not recorded	(33% of total cores)	No	(50%)	TRUS
PRIAS (13)	T2	<10	<0.2	3+3	10	2	No	Not recorded	No
University of Miami (14)	T2	<10	Not recorded	3+3	10	2	No	(20%)	No
Royal Marsden (15)	T2	<15	Not recorded	3+3 or	Not recorded	(<50% of total cores)	No	(50%)	Not mandatory
	>65 years old	<15	Not recorded	3+4	Not recorded	(<50% of total cores)	No	(50%)	Not mandatory
ProtecT (16)	Aged 50–69 years; clinically localised prostate cancer								
University of Toronto (17)	[1995–2013] T2a	<10	Not recorded	3+3	8	Not recorded	No	Not recorded	No
	[1995–1999] patients aged >70 years; [2000–2013] LE <10 years + significant morbidities	<15; 10–20	Not recorder; not recorded	3+4; 3+4	8; 8	Not recorded; not recorded	No; no	Not recorded; not recorded	No; no
University of Copenhagen (18)	T2a	<10	None recorded	3+3	6	3	No	Not recorded	No
St Vincents, Australia (19)	T2b [T2a (<55 years)]	<10	None recorded	3+3	10	<20% of total cores	No	6 mm (<30%)	No

Table 2 (*continued*)

Table 2 (*continued*)

Study	Maximum T score/age/life expectancy	PSA (μg/L)	PSA density ng/mL (PSAD)	Gleason score	Minimum number of cores taken pre-AS selection	Maximum No. of positive biopsy cores (% of total cores)	Additional confirmatory re-biopsy	MCL (percentage of biopsy core positive)	Imaging
Goteborg (20)	T1c (VLRPC)	Any	0.15	3+3	10 (6 up to 2009)	<3	No	(<50%)	No
	T1 (LRPC)	<10	–	3+3	10 (6 up to 2009)	Not recorded	No	Not recorded	No
	T2 (IRPC)	<20	–	3+4	10 (6 up to 2009)	Not recorded	No	Not recorded	No
Multi-institutional Canary PASS (21)	T1c (VLRPC)	–	<0.15	3+3	10 (within a year) or ×2 biopsies — one within a year	2	No	<50%	No
	T1c–T2a (LRPC)	<10 (LRPC)	–	3+3 (LRPC)	≥10 (within a year) or ×2 biopsies — one within a year	2	No	<50%	No
	T2b–T2c (IRPC)	10–20 (IRPC)	–	3+4 (IRPC)	≥10 (within a year) or ×2 biopsies — one within a year	2	No	<50%	No
	T2b–T2c (HRPC)	>20	–	3+4	≥10 (within a year) or ×2 biopsies — one within a year	2	No	<50%	No
Milan (SAINT + PRIAS) (22)	T1c–T2a (+T1b if cancer <0.5 cm^3 + negative peripheral zone biopsies) (SAINT)	<10	–	3+3	2005–2012—not recorded; Dec 2012–2016—prostate volume dependant (PV <40 cm^3 =8; 40–60 cm^3 =10; >60 cm^3 =12)	<20% of total cores (until Dec 2011) <25% of total cores [2011–2016]	No	<50%	No
	<T2c (PRIAS)	<10	<0.2	3+3 (3+4 if aged 70+)	Prostate volume dependant (PV <40 cm^3 =8; 40–60 cm^3 =10; >60 cm^3 =12)	<2% or <15% of total cores if saturation biopsies taken (>20 cores) with a maximum of 4 cores positive	No	<10% core length in 3+4 disease only	Yes since 2015—no limit on number of positive cores in patients with negative MRI or where targeted biopsy shows 3+3 disease only

LE, life expectancy; VLRPC, very low-risk prostate cancer; LRPC, low-risk prostate cancer; IRPC, intermediate-risk prostate cancer; HRPC, high-risk prostate cancer; SAINT, Sorveglianza Attiva Instituto Nazionale Tumori; MCL, maximum cancer length.

Table 3 Surveillance strategy

Study	DRE (frequency in months)	PSA (frequency in months)	Free to total ratio PSA (frequency in months)	General health assessment	Urinary symptoms assessment	Imaging	Number of biopsy cores	1st re–biopsy scheduled (frequency in months)	Follow–up biopsy schedule
MSKCC (10)	6/12	6/12	6/12	Yes	Yes	–	10–12	12–18/12	Every 2–3 years or change in DRE/sustained PSA rise
John Hopkins (11)	6/12	6/12	–	–	–	–	12	12/12	Annually
UCSF (12)	6/12	3/12	–	–	–	TRUS 6/12	12	9/12	Every 1–2 years
PRIAS (13)	–	3/12 (up to 2 years) then 6/12	–	–	–	–	Prostate volume dependant (PV <40 cm^3 =8; 40–60 cm^3 =10; >60 cm^3 =12)	12/12	Year 4 & 7
University of Miami (14)	3–4/12 (2 years) then 6/12	3–4/12 (up to 2 years) then 6/12	–	–	Yes (ICI–SF)	–	Not recorded	12/12 (after 2000–10/12 cores taken at 9/12)	Annually (earlier if a dramatic rise in PSA or change in DRE)
Royal Marsden (15)	3/12 (year 1), 4/12 (year 2) then every 6/12	3/12 (year 1), 4/12 (year 2) then every 6/12	–	Yes	–	–	10–12	24/12	Every 2 years
Protec T (16)	–	3/12 (up to 1 year) then 6–12/12	–	–	–	–	–	–	–
University of Toronto (17)	–	3/12 (up to 2 years) then 6/12	–	–	–	–	8–14	12/12	Every 3–4 years up to age 80
University of Copenhagen (18)	3/12	3/12	–	–	–	–	10–12	12/12	Variable depending on patient risk (PSAD)
St Vincents, Australia (19)	6/12 (3 years) then annually	3/12 (up to 3 years) then 6/12	–	–	–	–	–	12/12	At 1–2 years then every 3–5 years (switched to watchful waiting once age >75 years/ life expectancy <7 years)

Table 3 (*continued*)

Table 3 (*continued*)

Study	DRE (frequency in months)	PSA (frequency in months)	Free to total ratio PSA (frequency in months)	General health assessment	Urinary symptoms assessment	Imaging	Number of biopsy cores	1st re–biopsy scheduled (frequency in months)	Follow–up biopsy schedule
Goteborg (20)	3/12–6/12	3/12–6/12	–	–	–	–	–	No	Every 2–3 years or on clinical progression
Multi–institutional Canary PASS (21)	6/12	3/12	–	Yes	–	–	–	6/12–2/12	Year 2, 4, 6
Milan (SAINT + PRIAS) (22)	6/12 (SAINT)	3/12	–	–	–	–	Since 2012, Prostate volume dependant (PV <40 cm^3 =8; 40–60 cm^3 =10; >60 cm^3 =12)	12/12 then 24/12	Every 2 years
	6/12 (PRIAS)	3/12 (up to 2 years) then 6/12	–	–	–	–	Prostate volume dependant (PV <40 cm^3 =8; 40–60 cm^3 =10; >60 cm^3 =12)	12/12	Year 4 & 7

PSAD, PSA density; PSADT, PSA doubling time; PSAV, PSA velocity; TRUS, trans-rectal ultrasound; MCL, maximum cancer length; ICI-SF, international conference on incontinence short-form.

recommend serial serum PSA measurements, DRE and surveillance biopsies to check for and identify indications of tumour progression (*Table 3*).

DRE

Of the thirteen studies, DRE as part of the surveillance strategy played an important role in nine [MSKCC (10), John Hopkins (11) UCSF (12), University of Miami (14), Royal Marsden (15), University of Copenhagen (UCPH) (18), St Vincent's Australia (19), Goteborg (20) and Canary PASS (21)] with the frequency ranging from 3 to 6 monthly.

PSA

All studies carried out PSA testing, but again protocols ranged from 3 to 6 monthly. Only MSKCC (10) recommended a 6-monthly free to total ratio PSA as useful.

Prostate re-biopsy

Eleven studies carried out confirmatory biopsies within a year of initial diagnosis, whilst the Royal Marsden (15) cited acceptability within 2 years of AS initiation and ProtecT (16) required no repeat biopsy. All studies demonstrated differences in the frequency that biopsies were repeated thereafter. Two centres [John Hopkins (11) and University of Miami (12)] routinely biopsied annually, with the others ranging from 2–3 yearly or on clinical progression. Only the ProtecT study (16) did not perform routine and regular re-biopsy. UCSF (12) was the only institution to carry out regular trans-rectal ultrasound without biopsy.

General health assessment

Regular routine general health assessments were undertaken in two studies [MSKCC (10) and Canary PASS (21)], as a possible criterion for switching to watchful waiting (WW),

Table 4 Triggers for intervention (treatment or further characterisation)

Study	Gleason score	Positive cores No. (%)	MCL	PSAV	PSADT (yr)	DRE
MSKCC (10)	>6	>3	>50%			–
John Hopkins (11)	>6	(>33% of total cores)	>50%	–	–	–
UCSF (12)	>6	>2	–	–	<3	–
PRIAS (13)	>6	≥3		–	<3 (yearly repeat biopsies)	–
University of Miami (14)	>6	>2	Any increase in MCL	–	–	–
Royal Marsden (15)	≥4+3	(>50% of total cores)	–	>1 ng/mL per year	–	–
ProtecT (16)	50% in PSA increase triggered review					
University of Toronto (17)	Pathology upgrade	–	–	–	<3 (MRI or repeat biopsy undertaken)	–
University of Copenhagen (18)	≥4+3	>3	–	–	<3	–
St Vincents, Australia (19)	>6	(>20%)	>8 mm	>0.75	<3	T2b
Goteborg (20)	Any gleason or TNM upgrade	–	–	–	Any PSA progression	Any DRE change
Multi–institutional Canary PASS (21)	>6 (VLRPC, LRPC), >3+4 (IRPC, HRPC)	>2	(≥34%)	–	–	–
Milan (SAINT + PRIAS) (22)	>6 (SAINT)	>20% of cores (up to 2012), >25% cores [2012–2016]	>50%	–	<3	> T2c
	>6 (PRIAS)	>2	–	–	<3 (where PSADT 3–10 years and biopsy not within 12 months—additional biopsy indicated)	> T2c

LRPC, low-risk prostate cancer; IRPC, intermediate-risk prostate cancer; MRI, magnetic resonance imaging; MCL, maximum cancer length.

with only MSKCC indicating that they carried out regular lower urinary tract symptom assessment. Two centres [University of Toronto (17) and St Vincent's Australia (19)] indicated that they switched patients from AS to WW at 80 and 75 years old, respectively.

Triggers for intervention

At 5 years of follow-up, the proportion of men treated ranged from 14% to 50% across all of the studies. The proportion of men who developed metastatic disease was low across all studies, in the Johns Hopkins cohort (12) for example; this was recorded as 0.1% and 0.6% at 5 and 15 years, respectively. The PC specific mortality rates were also low ranging from 0.2% to 5.7% (10,17) (*Table 1*).

Definitions of disease reclassification and progression differ across national guidelines and the AS cohorts described here are different. Many of the cohorts describe changes in one or multiple criteria for initiation of definitive treatment (*Table 4*).

Pathology (Gleason score)

Amongst the 13 cohorts reviewed here, 8 studies [MSKCC (10), John Hopkins (11), UCSF (12), PRIAS (13), University of Miami (14), St Vincent's Australia (19), Canary PASS (21) and Milan (22)] triggered intervention in LRPC if subsequent pathology was Gleason score >6. In the Canary PASS LRPC group radical treatment versus continued AS (with re-classification as intermediate-risk) were discussed as options. Two [University of Toronto (17) and Goteborg (20)]

suggested any pathological upgrade would trigger intervention. Two cohorts [Royal Marsden (15) and UCPH (18)] identified a Gleason score of ≥4+3 as the trigger point. Only Canary PASS (21) and Goteborg (20) gave a weighting depending on very low-risk/low risk (Gleason >3+3) or intermediate/High-risk (Gleason ≥3+4) disease.

Number/percentage of positive cores

Five of the thirteen studies [MSKCC (10), UCSF (12), PRIAS (13), University of Miami (14) and Milan (22)] maintained that >2 cores positive should trigger treatment, with the UCPH (18) extending this to >3 cores positive. St Vincent's Australia (19) suggested that cancer found in >20% of any positive core should trigger intervention, whilst The Royal Marsden (15) and Johns Hopkins (11) suggested a higher threshold for triggering treatment: 50% and 33% respectively. The remaining studies gave no indication of cut-off based on number of cores positive. The maximum cancer length (MCL) was variable, with two centres [MSKCC (10) and John Hopkins (11)] suggesting a cut-off of 50% and two centres suggesting more conservative numbers; St Vincent's Australia (19) suggesting a cut-off of 8 mm of cancer and the Canary PASS consortium was set at ≥34%. The University of Miami (14) defined any increase in volume of PC and in MCL as their trigger for intervention.

PSA-based triggers for intervention included PSA doubling time (PSAD) and PSA velocity (PSAV). Only two studies suggested PSAV as an important trigger, The Royal Marsden (15) suggesting a PSAV of >1 and St Vincent's Australia (19) >0.75. PSA doubling time was included in six studies [UCSF (12), PRIAS (13), University of Toronto (17), UCPH (18), St Vincent's Australia (19) and Milan (22)] with a cut-off of 3 years. The Goteborg group (20) defined the trigger as any PSA progression.

Summary of systematic review

The thirteen AS cohorts included in this review demonstrated a wide variety of descriptions of LRPC. This indicates a clear lack of consensus on defining favourable risk disease, suitability for AS and intervention thresholds.

Patient selection (*Table 2*): despite all studies agreeing that a clinically localised PC diagnosis was defined as T2 disease and the majority of studies agreeing on a PSA threshold of <10 µg/L and Gleason score 3+3 (3+4 in intermediate risk disease), there was significant inconsistency in practice when considering pathology (i.e., the number of acceptable positive cores and MCL).

Monitoring protocols (*Table 3*): all studies agreed on PSA surveillance with a frequency ranging from 3 to 6 monthly and most agreed that a confirmatory biopsy was required within 12 months after AS selection, however, no consensus was reached on the importance and relevance of DRE or re-biopsy strategy.

Triggers for intervention (*Table 4*): the cohorts described here appear cautious in their definition of disease progression, with low tolerance for increasing PSA defined as "any" or number of positive cores, cancer volume, and/or change in Gleason score. There was no universal agreement on triggers for intervention although, agreement was reached on Gleason score >6 in 62% of studies, number of percentage increase in positive cancer cores was identified in 69% of the cohorts, MCL and PSA doubling time of <3 years was used in 46% of the studies.

A narrative review performed in 2016 showed that existing guidelines regarding AS for PC vary widely, but predominantly state that the most suitable patients for AS are those with pre-treatment clinical stage T1c or T2 tumours, serum PSA levels <10 µg/L, biopsy Gleason scores of ≤6, a maximum of two tumour positive biopsy core samples and/or a MCL of 50% per core sample (44). The heterogeneity in practice demonstrated in this narrative, further highlights the need for a robust collaborative worldwide prospective study to finally determine safe patient selection, monitoring and appropriate triggers for intervention.

The future of AS

Imaging

The use of magnetic resonance imaging (MRI) in the context of AS varies between practitioners, countries and healthcare systems. Current European (45) guidance on prostate MRI concentrates on its role in the detection and staging of PC. Little evidence has yet been published supporting more generalised use in the context of AS.

This may explain why only two of the thirteen cohorts reviewed [the Milan arm of the PRIAS study (22) and University of Toronto] used MRI to support AS at the time of reporting. The Milan group used MRI imaging routinely (from 2015) as an adjuvant to the AS selection criteria, opening up AS selection to men with negative MRI scans. No limit was placed on number of positive cores in patients with negative MRI's or where targeted biopsy shows

3+3 disease only. The University of Toronto used MRI as a conduit to triggering intervention. Where patients had a PSADT of <3 years, MRI and/or repeat biopsy was used to clarify the need for treatment.

In 2015 a systematic review of MRI use in AS found only seven studies addressing MRI reliability in relation in selecting patients for AS using biopsy correlation and two studies focused on the use of repeat MRI in AS (46). This review was hampered by the small number of patients in the included studies as well as the low number of studies. It was concluded that MRI could detect clinically significant PC, however as of yet MRI cannot be considered as an alternative to repeat biopsy in long-term monitoring on AS without further evidence from robust prospective studies.

Despite the paucity of evidence, in 2014 the UK National Institute for Heath and Care Excellence (NICE) PC guidelines (8) suggested a role for MRI in AS, but without any guidance on the criteria for radiological significance and progression. With this in mind, the European School of Oncology recently reported the PRECISE recommendations (47) for MRI usage in AS, with the aim of facilitating the development of a robust evidence base for documenting changes in prostate MRI findings in men on AS over time. This checklist will allow for better assessment of the natural history of MRI change in men on AS.

The role of nomograms in AS

Nomograms have been successfully used and integrated into healthcare setting as an assist to both patients and clinicians in establishing risk and aiding decision making. There is widely accepted usage of nomograms in PC diagnosis (48,49). However, predictive nomograms for indolent disease in the context of AS have been less successful (50). In 2016 Venderbos and colleagues studied participants of the European Randomized study of Screening for PC (ERSPC) (51) to establish whether a probabilistic nomogram could improve patient selection for AS compared to a rule based criteria. They reviewed men initially diagnosed with histopathological indolent PC at radical prostatectomy [defined as pT2, Gleason pattern ≤3 and tumour volume (TV) ≤0.5 mL or TV ≤1.3 mL] to develop an existing nomogram to provide probability-based data and compared this to rule-based selection according to the PC Research International: Active Surveillance (PRIAS) (13), University of Toronto (17), and Johns Hopkins (11) criteria. The performance of the nomogram, using the Johns Hopkins (11) and PRIAS (13) rule-based criteria's, were found to be comparable and could prove a good alternative to rigid rule-based surveillance protocols where patients request more information on probability of progression to make informed decisions on treatment.

Global action plan PC active surveillance (GAP3) initiative

Although AS has evolved to a broadly accepted management strategy for men diagnosed with LRPC, this systematic review of worldwide AS practices confirms there is little consensus on inclusion criteria, surveillance schedules and intervention thresholds. Also, variation in AS semantics used in literature and guidelines could lead to confusion.

To address these issues, the Movember Foundation launched within their Global Action Plan Prostate Cancer Active Surveillance initiative (GAP3) in August 2014 (52). To date, GAP3 has united as many as 25 institutions, hospitals and research centres from the USA, Canada, Australia, Singapore, Japan, Korea, UK, Ireland, the Netherlands, France, Sweden, Finland, Switzerland, Italy and Spain. The primary aim of the GAP3 initiative is to create global consensus on the selection and monitoring of men with low risk PC, ultimately resulting in worldwide uniform guidelines.

Within the GAP3 initiative, the largest centralized PC AS database to date was constructed by combining patient data from 25 established AS cohorts worldwide. This database currently comprises clinical, marker-related and imaging data on more than 15,000 patients. Multiple data analyses of this unique global data set are currently ongoing focussing on three main questions regarding AS: which patients are most suitable for AS, what is the most appropriate follow-up schedule and what is the right moment to switch to active treatment? Based on these results, a peer reviewed publication on consensus guidelines is expected in 2019.

In addition, the GAP3 programme is performing a centralized pathology review of randomly selected biopsies. Preliminary results confirm consistent biopsy quality and grading across the different centres, which would enable data analyses without correction. Moreover, a panel of leading PC specialists in the field of AS was convened to overcome the AS semantic heterogeneity in literature and guidelines (43). By using a modified Delphi consensus procedure including a three-round sequence of online questionnaires and a face-to-face consensus meeting, formal consensus was reached for all 61 individual terms.

Movember has recently allocated additional funding to maintain the database and update the clinical data

annually with a special focus on MRI, quality of life and genomics data. MRI is becoming an increasingly important technology for the management of AS. GAP3 aims to also assess the value of MRI with respect to lesion definition and changes over time. Conclusions based on the analyses of patient series published to date are limited due to small size cohorts. Therefore, the need to combine these data is imperative to assess the value of MRI. This also holds true for assessing the use of genomic markers, as well as quality of life in the decision to initially pursue AS rather than active treatment.

In summary, analyses of global AS data within GAP3 will further elucidate the optimal inclusion criteria, surveillance schedules and intervention thresholds and result in more uniform AS guidelines.

This will enable clinicians to more confidently identify men who are suitable for AS and to also decide whose PCa has progressed and will, therefore, require treatment. In addition, this will reassure men of making the most informed treatment decision for their type of disease.

Conclusions

In the last 15 years large cohort studies have progressed the definition of safe AS. Collaborations between institutions [ProtecT (UK) (16) and Canary PASS (US) (21)] and even countries [The PRIAS study (13)] have contributed to our increasing confidence in AS and a demonstrable increase in the number of men selecting AS.

This systematic review shows that AS is being applied. However, implementation of successful AS programmes worldwide needs to reduce the over treatment of PC as well as creating a safety net for men incorrectly diagnosed with indolent disease. Currently, the general Urologist and/or Oncologist may struggle to manage these patients with any degree of confidence, which may explain variations in practice. This confidence requires robust data from large cohorts with long follow-up, such as collected within the GAP3 initiative, to create global consensus on inclusion criteria, surveillance schedules and intervention thresholds.

Acknowledgements

Funding: Sigrid Carlsson is supported in part by a Cancer Center Support Grant from the National Cancer Institute made to Memorial Sloan Kettering Cancer Center (P30-CA008748), a SPORE grant from the National Cancer Institute to Dr. H. Scher (P50-CA092629), a grant from the National Cancer Institute as part of the Cancer Intervention and Surveillance Modeling Network (U01CA199338-02) and the David H. Koch prostate cancer research fund.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Kinsella N, Helleman J, Bruinsma S, Carlsson S, Cahill D, Brown C, Van Hemelrijck M. Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. Transl Androl Urol 2018;7(1):83-97. doi: 10.21037/tau.2017.12.24

10.6. Appendix 6 2014 NICE Guidelines for Active Surveillance Management - UK

Prostate cancer
Protocol for active surveillance

NICE National Institute for Health and Care Excellence

Timing	Tests[1]
At enrolment in active surveillance	• Multiparametric MRI if not previously performed
Year 1 of active surveillance	• Every 3–4 months: measure PSA[2] • Throughout active surveillance: monitor PSA kinetics[3] • Every 6–12 months: DRE[4] • At 12 months: prostate rebiopsy
Years 2–4 of active surveillance	• Every 3–6 months: measure PSA[2] • Throughout active surveillance: monitor PSA kinetics[3] • Every 6–12 months: DRE[4]
Year 5 and every year thereafter until active surveillance ends	• Every 6 months: measure PSA[2] • Throughout active surveillance: monitor PSA kinetics[3] • Every 12 months: DRE[4]

[1]If there is concern about clinical or PSA (prostate-specific antigen) changes at any time during active surveillance, reassess with multiparametric MRI and/or rebiopsy.

[2]May be carried out in primary care if there are agreed shared-care protocols and recall systems.

[3]May include PSA doubling time and velocity.

[4]Should be performed by a healthcare professional with expertise and confidence in performing DRE (digital rectal examination).

https://www.nice.org.uk/guidance/cg175/resources/protocol-for-active-surveillance-191674477

10.7. Appendix 7 European Urology paper

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Review – Prostate Cancer

Editorial by Jenny L. Donovan and Freddie C. Hamdy on pp. 281–282 of this issue

Factors Influencing Men's Choice of and Adherence to Active Surveillance for Low-risk Prostate Cancer: A Mixed-method Systematic Review

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Article info

Article history:
Accepted February 26, 2018

Associate Editor:
Matthew Cooperberg

Keywords:
Active surveillance
Treatment choice
Adherence
Prostate cancer
Facilitators
Barriers
Treatment selection
Chronic disease adherence

Abstract

Context: Despite support for active surveillance (AS) as a first treatment choice for men with low-risk prostate cancer (PC), this strategy is largely underutilised.
Objective: To systematically review barriers and facilitators to selecting and adhering to AS for low-risk PC.
Evidence acquisition: We searched PsychINFO, PubMed, Medline 2000-now, Embase, CINAHL, and Cochrane Central databases between 2002 and 2017 using the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement. The Purpose, Respondents, Explanation, Findings and Significance (PREFS) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) quality criteria were applied. Forty-seven studies were identified.
Evidence synthesis: Key themes emerged as factors influencing both choice and adherence to AS: (1) patient and tumour factors (age, comorbidities, knowledge, education, socioeconomic status, family history, grade, tumour volume, and fear of progression/side effects); (2) family and social support; (3) provider (speciality, communication, and attitudes); (4) healthcare organisation (geography and type of practice); and (5) health policy (guidelines, year, and awareness).
Conclusions: Many factors influence men's choice and adherence to AS on multiple levels. It is important to learn from the experience of other chronic health conditions as well as from institutions/countries that are making significant headway in appropriately recruiting men to AS protocols, through standardised patient information, clinician education, and nationally agreed guidelines, to ultimately decrease heterogeneity in AS practice.
Patient summary: We reviewed the scientific literature for factors affecting men's choice and adherence to active surveillance (AS) for low-risk prostate cancer. Our findings suggest that the use of AS could be increased by addressing a variety of factors such as information, psychosocial support, clinician education, and standardised guidelines.

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https://doi.org/10.1016/j.eururo.2018.02.026
0302-2838/

1. Introduction

Prostate cancer (PC) accounts for 400 000 new cancer cases in Europe [1] and 160 000 in the USA [2] annually. Rapid uptake of prostate-specific antigen (PSA) testing and better diagnostic procedures have led to a significant stage migration with earlier diagnosis of localised, low-risk PC (LRPC), ranging from 10% to 80% of all men diagnosed with PC worldwide [3–5]. A large proportion of these men do not require immediate radical treatment, but can be monitored using blood tests, digital rectal examination, prostate biopsy and/or multiparametric magnetic resonance imaging (MRI)— an approach known as active surveillance (AS) [5].

While there are no universally agreed upon selection criteria for AS, the authors of a recent review of currently used guidelines worldwide agreed on the following criteria, consistent with the definition of very LRPC: clinical stage T1c–T2a, PSA <10 ng/ml, biopsy Gleason score 6, maximum 1 or 2 positive biopsy cores, and/or maximum 50% of cores with cancer [6].

Large cohort studies (Supplementary material, Overview of large cohort active surveillance studies) reporting over the last 5 yr have shown little physical morbidity and low PC-specific mortality while on AS: 0.1–5.7% over 10–15 yr [7,8], observations that have recently contributed to an increased uptake of this management strategy [5,9].

AS uptake continues to vary across countries and practices, and among physicians [10]. This was most noticeable in the US Cancer of the Prostate Strategic Urologic Research Endevour (CaPSURE) database, which reported a sharp rise in the uptake of AS, from 10% over the past 2 decades to 40% in 2010–2013 [5], and the Swedish National Prostate Cancer Register (NPCR), which noted a rise from 40% to 74% between 2009 and 2014 [11]. In Australia, where the healthcare culture is fairly evenly split between private and public systems, a 25% overall recruitment to AS was recorded by the Victorian PC Registry during the period 2008–2012 [12]. However, in Sweden, where healthcare is delivered largely by the public sector, the proportion of men selecting AS was significantly higher (80–90% of eligible men) [11]. Understanding the drivers for this variation in practice is essential.

In cohort studies reporting on AS adherence, a large proportion of men continue to drop out of AS, despite no evidence of disease progression (Supplementary material, Overview of large cohort active surveillance studies). Much research has focused on the influence of anxiety and depression on adherence. Cancer Research UK describes depression as an established response to a diagnosis of cancer, unrelated to stage or severity [13]. However, in PC the risk of moderate to severe depression (requiring treatment) has been reported as relatively low in comparison with other tumour groups, at 5% [14].

There is thus a need to identify and understand the barriers and facilitators to AS. This would then provide means for future research themes to study interventions aimed at increasing both uptake of and adherence to AS. The purpose of this paper is, therefore, to systematically evaluate the literature for factors affecting choice and adherence to AS as a PC management strategy for LRPC.

2. Evidence acquisition

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [15].

2.1. Search strategy

Studies published between 2002 (when AS was first described in the literature [16]) and December 2017 were identified through a systematic search of electronic databases (PsychINFO, PubMed, Medline 2000-now, Embase, CINAHL, and Cochrane Library; Fig. 1). The search strategy focused on the use of keyword search terms to identify studies based on PC AS: prostate cancer OR prostatic neoplasm, active surveillance OR watchful waiting, facilitators OR barriers, treatment adherence OR treatment compliance, treatment OR therapy OR therapeutics, and decision making. The full search strategy is identified in Figure 2. References were also searched for eligible publications.

2.2. Study eligibility and selection

Eligible studies for inclusion in the final analysis were those that evaluated choice and/or adherence to AS rather than watchful waiting (WW). Although there are similarities between choice of AS and WW, they are conceptually different management strategies (AS is a strategy employed to monitor a patient where there is intention to offer radical treatment with curative intent when/if required; WW implies no intention to offer curative treatment). Hence, studies where AS and WW subgroups were combined were excluded to reduce bias.

We considered studies eligible if they were original articles with a qualitative or quantitative design generating data on decision making in LRPC when AS was considered a primary treatment option. Eleven studies were excluded on the basis of poor study quality or mixed WW/AS subgroup [17], as were qualitative studies that failed to state that saturation of information had been reached (usually ≥20 participants). Inclusion of at least 20 participants in a study is a general guideline in qualitative research to reach data saturation [18]. One study that fell beneath this threshold was included as information saturation was demonstrated.

Cohort/registry studies were included when they were multi-institutional and included >500 patients to reduce the associated risk of bias in small sample sizes and increase the external validity and generalisability. Studies reporting on AS adherence also included ≥2 yr of follow-up.

2.3. Data quality

Qualitative and mixed-methodology studies were evaluated for quality using the Purpose, Respondents, Explanation, Findings and Significance (PREFS) quality checklist. This checklist was developed by Joy and Bridges [17] for assessing quality of reports in systematic reviews of literature on patient preferences and comprises questions

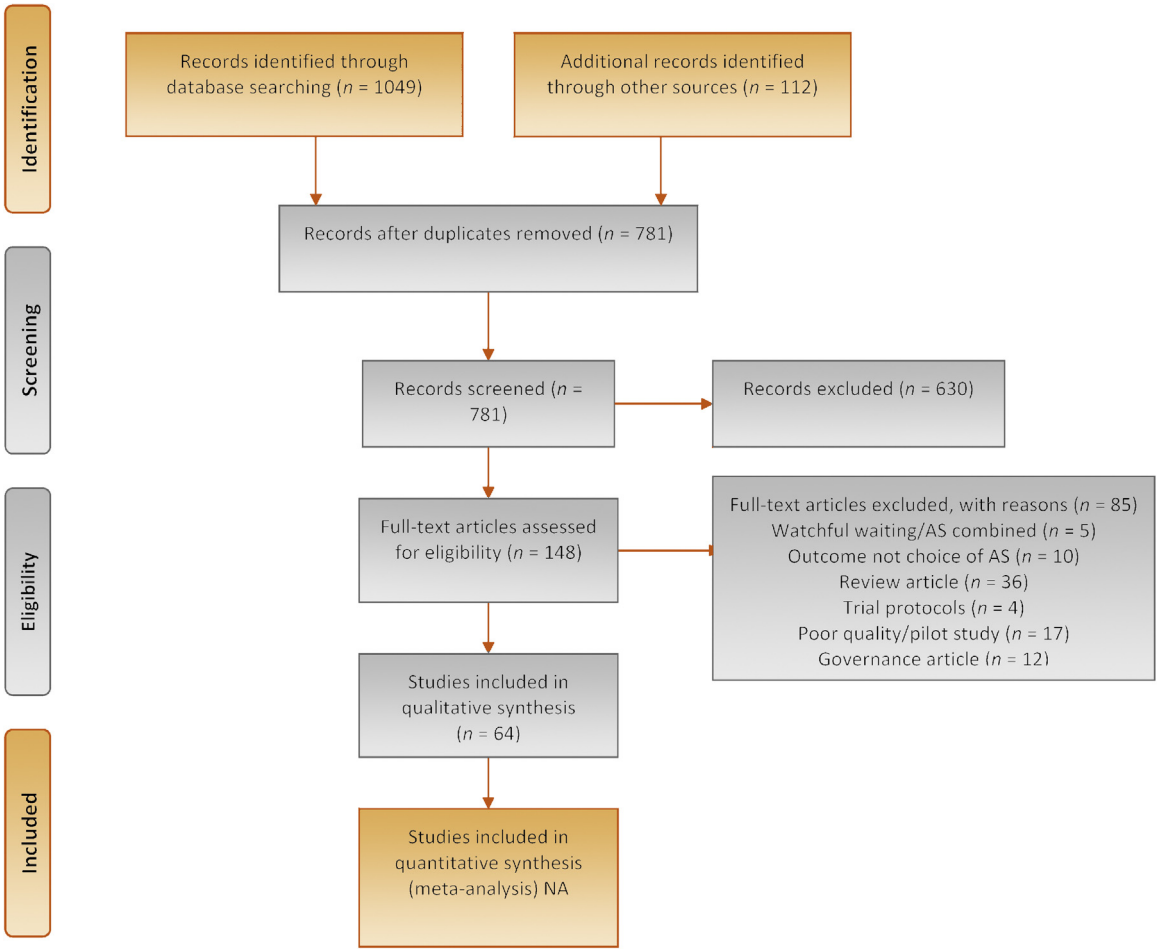

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) flow diagram. AS = active surveillance; NA = not available.

Prostate cancer:

("prostate cancer" OR "Prostatic Neoplasms" [MeSH])

Active surveillance:

("active surveillance" OR "Active Surveillance" OR "watchful waiting" OR "Watchful Waiting [MeSH])

Barriers/facilitators:

("facilitators"[ti] OR "barriers*"[ti] OR "treatment adherence*"[ti] OR "treatment choice""[ti] OR "treatment selection"*[ti] OR "treatment compliance*"[ti] OR ((treatment[ti] OR therapy[ti] OR "Therapeutics" [MeSH]) AND "decision making" [MeSH])))*

Fig. 2 – Search strategy.

regarding five aspects of each study: purpose (P), respondents (R), explanation (E), findings (F), and significance (S). The complete PREFS checklist is shown in Table 1. The PREFS checklist in the Supplementary material outlines the quality questions. A quality score was calculated by adding one point for each "yes" answer on the PREFS checklist, with a maximum potential score of 5. Papers were categorised in a way similar to that reported by Joy et al [17]: standard gamble (SG, ie, health-related quality of life [HRQoL])—17 papers; contingent evaluation (CO; ie, survey)—14 papers; stated preference other (SPO; ie, monetary value or choices or ratings)—three papers; qualitative (ie, interviews)—13 papers; and three papers with mixed methodology.

The mean PREFS quality score was 3.46 (standard deviation [SD] 0.54), and the scores ranged from 2 to 5. The mean quality scores were 3.15 (SD 0.55) in studies with qualitative methods, 3.33 (SD 0.57) in studies with SPO methods, 3.76 (SD 0.44) in studies with CO methods, 3.58 (SD 0.51) in studies with SG methods, and 3 (SD 0) in studies with mixed methodology. Forty-six studies explicitly stated that the purpose (P domain) of the study was to evaluate factors effecting choice or adherence to AS, and 31 studies

Table 1 – Purpose, Respondents, Explanation, Findings, and Significance checklist

Study (publication date), place	Quality score	Purpose (P)	Respondents (R)	Explanation (E)	Findings (F)	Significance (S)	Category of paper
Davison and Breckon (2012) [32], Canada	4	Yes	Yes	Yes	No	Yes	CO
Goh et al (2012) [50], USA	3	Yes	Yes	Yes	No	No	CO/Q
Orom et al (2014) [51], USA	4	Yes	Yes	Yes	No	Yes	CO
Xu et al (2016) [27], USA	4	Yes	Yes	Yes	No	Yes	CO
Orom et al (2017) [33], USA	4	Yes	Yes	Yes	No	Yes	CO
Anandadas et al (2011) [25], UK	3	Yes	Yes	No	No	Yes	SG
Gorin et al (2011) [41], USA	3	Yes	No	Yes	Yes	No	CO
Loeb et al (2017) [52], USA	3	Yes	No	Yes	Yes	No	Q
Volk et al (2014) [40], USA	3	Yes	Yes	Yes	No	No	Q
Xu et al (2012) [45], USA	3	Yes	No	Yes	Yes	No	Q
O'Callaghan et al (2014) [46], Australia	3	Yes	No	Yes	Yes	No	Q
Mishra et al (2013) [47], USA	3	No	No	Yes	Yes	Yes	SPO
Ehdaie et al (2017) [44], USA	4	No	Yes	Yes	Yes	Yes	SPO
Venderbos et al (2015) [82], The Netherlands	4	Yes	No	Yes	Yes	Yes	SG
Venderbos et al (2017) [67], Europe	4	Yes	No	Yes	Yes	Yes	SG
Lang et al (2017) [31], USA	4	Yes	No	Yes	Yes	Yes	CO
Kendel et al (2016) [79], Germany	4	Yes	Yes	Yes	No	Yes	CO
Vasarainen et al (2012) [65], Helsinki	4	Yes	No	Yes	Yes	Yes	SG
Bellardita et al (2013) [60], Italy	4	Yes	No	Yes	Yes	Yes	SG
Vanagas et al (2013) [66], Lithuania	3	Yes	No	Yes	No	No	SG
Hegarty et al (2008) [61], USA and Ireland	3	Yes	No	Yes	Yes	No	SG
Smith et al (2009) [79], Australia	3	Yes	No	Yes	Yes	No	SG
Parker et al (2016) [63], USA	4	Yes	Yes	Yes	No	Yes	SG
Punnen et al (2013) [14], USA	4	Yes	Yes	Yes	No	Yes	SG
Lane et al (2016) [75], UK	4	Yes	Yes	Yes	No	Yes	CO
Van den Bergh et al (2010) [71], The Netherlands	4	Yes	No	Yes	Yes	Yes	SG
Xu et al (2011) [81], USA	4	Yes	No	Yes	Yes	Yes	Q
Xu et al (2016) [78], USA	4	Yes	Yes	Yes	No	Yes	CO
Wilcox et al (2014) [62], Australia	4	Yes	No	Yes	Yes	Yes	SG
Burnet et al (2007) [72], UK	4	Yes	No	Yes	Yes	Yes	SG
Davison and Goldenberg (2011) [73], Canada	3	Yes	No	Yes	No	No	CO
Anderson et al (2014) [74], Australia	3	Yes	Yes	No	No	Yes	SG
Oliffe et al (2009) [59], Canada	3	Yes	Yes	No	yes	No	CO
Berger et al (2014) [85], USA	3	Yes	Yes	No	No	Yes	Q
Seiler et al (2012) [86], USA	4	Yes	No	Yes	Yes	Yes	CO
Kinsella et al (2015) [88], UK	3	No	Yes	No	Yes	Yes	SPO
Wade et al (2015) [48], UK	3	Yes	No	Yes	Yes	No	CO/Q
Kazer et al (2011) [55], USA	4	Yes	No	Yes	Yes	Yes	Q
Wade et al (2013) [49], UK	3	Yes	No	Yes	Yes	No	SG
Wade et al (2015) [89], UK	3	Yes	No	Yes	Yes	No	Q
Latini et al (2007) [80], USA	4	Yes	Yes	No	Yes	Yes	CO
Jeldres et al (2015) [64], USA	3	Yes	No	Yes	No	Yes	SG
Donovan et al (2016) [68], UK	4	Yes	No	Yes	Yes	Yes	SG
Loeb et al (2017) [83], USA	33	Yes	No	Yes	Yes	No	Q
Le et al (2016) [43], USA	3	Yes	No	Yes	Yes	No	Q
Scherr et al (2017) [53], USA	3	Yes	No	Yes	Yes	Yes	Q/SG/CO
Taylor et al (2016) [28], USA	4	Yes	No	Yes	Yes	Yes	Q
Mader et al (2017) [42], USA	3	Yes	No	Yes	Yes	No	Q
Lyons et al (2017) [56], USA	2	Yes	No	Yes	No	No	Q
Chen et al (2017) [69], USA	4	Yes	Yes	Yes	Yes	No	CO

CO = contingent evaluation (survey); Q = qualitative (interviews); SG = standard gamble (health-related quality of life); SPO = stated preference (other) – (monetary value or choices or ratings).

included all respondents in the evaluation of findings (F domain). There was more variability among the studies in satisfying the R, E, and S domains of the PREFS checklist, demonstrating that many reports lacked details regarding whether responders were similar to nonresponders and failed to include statistical tests to evaluate results where possible.

The included cohort/registry epidemiology papers were assessed for strength of evidence. Although no quality assessment tool completely fitted the purpose of this review, assessments were made using a modified Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist [19] (Table 2). The following items were assessed: number of participants, variables (clear explanation of all outcomes, exposures, potential confounders, and effect modifiers), data source (details given of measurement), bias (effort made to address potential sources of bias), statistical methodology (description of methods, missing data addressed, and sensitivity analysis performed), descriptive data (characteristics of individuals given: demographic, clinical, and social), and limitations (generalisability addressed and cautious interpretation). In each of the seven categories, one point was assigned to each positive response, giving a possible total score of 12.

Table 2 – Strength of confidence in quality of quantitative cohort/registry studies (modified STROBE checklist)

Author (year), place	Variables documented				Bias			Statistical methodology			Descriptive data			Limitations	Score
	Outcome	Exposure	Confounders and modifiers	Documented	Addressed	Full description	Missing data	Sensitivity analysis	Demographic	Clinical	Social				
Aizer et al (2012) [22], USA	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	10
Loeb et al (2013) [24], Sweden	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Filson et al (2014) [37], USA	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Hoffman et al (2014) [37], USA	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	9
Liu et al (2015) [26], USA	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Maurice et al (2015) [35], USA	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	8
Womble et al (2015) [23], USA	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Loeb et al (2017) [11], Sweden	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	11
Loeb et al (2015) [29], Sweden	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	9
Hamdy et al (2016) [30], UK	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	10
Bokhorst et al (2015) [93], The Netherlands	Yes	Yes	Yes	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	6
Weerakoon et al (2015) [12], Australia	Yes	Yes	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	8
Parikh et al (2017) [36], USA	Yes	No	Yes	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8
Bokhorst et al (2016) [92], worldwide	Yes	Yes	No	No	No	Yes	No	No	No	No	Yes	Yes	No	Yes	5

STROBE = Strengthening The Reporting of Observational Studies in Epidemiology.
Variables (clear explanation of all outcomes, exposures, potential confounders, and effect modifiers), data source (details given of measurement), study size (≥500 patients), bias (effort made to address potential sources of bias), statistical methodology (description of methods, missing data addressed, and sensitivity analysis performed), descriptive data (characteristics of individuals given: demographic, clinical, and social), and limitations (generalisability addressed, cautious interpretation) were assessed.

The mean quality score was 8.78 (SD 1.8). The scores ranged from 5 to 11. All studies included outcome variables, a full description of statistical methodology, clinical data, and limitations. The highest level of variability was found in relation to bias, missing data, and sensitivity analysis. Five papers scored ≥10.

3. Evidence synthesis

We identified 1049 unique citations; of these 901 were excluded as review articles, commentaries, or narratives. Full-text screening was carried out on 148 articles, of which 85 were excluded, rendering 64 articles included for synthesis. Given the heterogeneous study designs, no statistical comparisons were made.

This mixed-method systematic review uses a modified version of the Joanna Briggs Institute—Methodology for JBI Mixed Methods Systematic reviews (integrated approach) [20]. Joanna Briggs Institute integrated methodology combines both qualitative and quantitative data into a single mixed-method synthesis [20]. A meta-aggregation of data is presented using a Bayesian approach, whereby all data were codified into themes and then presented in a meta-aggregation. This approach generates summative statements of the evidence to equally inform the topic in a mutually compatible format [21], as seen in Table 2. The six themes identified were as follows: cancer characteristics, patient, family and social support, provider, healthcare organisation/practice, and health policy.

Three authors (N.K., M.V.H., and S.C.) independently screened all titles and abstracts. The resulting reference list was compiled for full-text screening and data extraction. The final reference list was screened and agreed by all authors. A data abstraction form was developed for both qualitative and quantitative studies, based on review of the first articles of each type from among the selected papers. One author (N.K.) extracted data onto a spreadsheet, which was checked by two other authors (S.C. and M.V.H.). Data abstraction was performed separately by two reviewers (N. K. and S.C. or M.V.H.). Data extraction included publication year, authors, journal name, title, study design, setting, population, eligibility criteria for participants, data collection method, response rate, and outcomes (Table 1). The review of findings/themes was open ended with no prespecified coding system, with intent to describe the primary conclusions of the authors.

3.1. *Study design of included studies*

Table 3 summarises the 64 included studies. Thirty-seven studies took place in North America, 20 in Europe, and five in Australia; one compared America with Ireland; and one was a worldwide study. The total number of study participants was 452 4560, ranging from 7 to 189 768 in each study. The average age at diagnosis across the studies was 65 yr.

The assessments were reported between 2007 and 2017. The studies consisted of 13 surveys, 12 qualitative interviews/focus groups, 12 cohort/registry studies, two

Table 3 – Overview of the studies included in the systematic review on factors affecting choice and adherence to active surveillance in men with low-risk prostate cancer

#	Author	Year	Reference	Design	*N* or Response rate (%)	Country	Study population/ setting	Data collection method (instrument)	Study period	Age (mean)
1	Davison and Breckon	2012	[32]	Cross-sectional survey to AS patients	180/258 (70%)	Canada	Clinical/hospital	Survey (Likert scale)	2009–2011	67
2	Goh et al	2012	[50]	Cross-sectional survey to AS patients	34/34 (100%)	USA	Research/support group	Survey/interviews	May–August 2011	63
3	Orom et al	2014	[51]	Cross-sectional survey to AS patients	120/126 (79%)	USA	Clinical/hospital	Survey	2010–2012	65
4	Xu et al	2016	[27]	Cross-sectional survey to patients with localised PC	260/559 (68%)	USA	Population database	Survey	2009–2010	61
5	Orom et al	2017	[33]	Prospective survey of patients undergoing AS/RP/RT	1531/3337 (46%)	USA	Database/hospital	Survey (distress thermometer—11-point analogue scale)	2010–2014	Unknown
6	Anandadas et al	2011	[25]	Prospective survey to AS patients	768/768 (100%)	UK	Clinical/hospital	Survey (RAND-36 Item—SF-36v.2, UCLA-PCI, study-specific survey)	2000–2006	65
7	Gorin et al	2011	[41]	Prospective survey to AS patients	105/185 (57%)	USA	Clinical/hospital	Survey	Unknown	66
8	Loeb et al	2017	[52]	Qualitative interviews with PC clinicians	24	USA	Hospital/community	Interviews (thematically analysed)	July–December 2015	NA
9	Volk et al	2014	[40]	Qualitative interviews with AS patients and RP/RT patients	30/36 (83%)	USA	Clinical/hospital	Interviews (thematically analysed)	2011	63
10	Xu et al	2012	[45]	Qualitative interviews with patients with LRPC	21	USA	Research/clinical community	Interviews (thematically analysed)	Unknown	58
11	Interviews			O'Callaghan et al (thematically analysed and inter-rated)	2014 2012–2013	[46] Range 61–70	Qualitative interviews with patients with LRPC and their partners	21 men and 14 partners	Australia	Clinical/ hospital and community
12	Aizer et al	2012	[22]	Retrospective cohort/registry study	701	USA	Clinical/hospital	Database	Unknown	62
13	Loeb et al	2013	[24]	Retrospective cohort/registry study	57 713	Sweden	Population database	Database	1998–2011	65
14	Filson et al	2014	[37]	Retrospective cohort/registry study	7347	USA	Population database	Database	2004–2007	66+
15	Hoffman et al	2014	[34]	Retrospective cohort/registry study	12 068	USA	Population database	Database	2006–2009	66
16	Liu et al	2015	[26]	Retrospective cohort/registry study	609	USA	Population database/ hospital and community	Database	2012–2013	65
17	Maurice et al	2015	[35]	Retrospective cohort/registry study	189 768	USA	Population database	Database	2010–2011	Unknown
18	Womble et al	2015	[23]	Retrospective cohort/registry study	682	USA	Population database/ hospital and community	Database	2012–2013	63
19	Loeb et al	2017	[11]	Retrospective cohort/registry study	32 518	Sweden	Population database	Database	2009–2014	67
20	Mishra et al	2013	[47]	Content analysis of patient's Internet conversations	464	USA	Internet conversations	Qualitative software (sentiment index)	2002–2012	Unknown
21	Ehdaie et al	2017	[44]	Prospective counselling intervention to physicians	5 surgeons; 1003 patients	USA	Clinical/hospital	Database and survey	2014–2015	60
22	Venderbos et al	2015	[82]	Retrospective survey comparing anxiety and distress at 0, 9, and 18 mo on AS	150 (86%, 90%, and 96% at 0, 9, and 18 mo)	The Netherlands	Clinical/hospital	Survey (CES-D Scale, MAX-PC, STAI-6, DCS)	2007–2008	Unknown
23	Venderbos et al	2017	[67]	Retrospective survey comparing HRQoL in treatment groups: AS, RP, RT to matched patients	879 (65–75%)	Europe	Clinical/hospital	Survey (EPIC, SF-12, STAI-6, EQ-VAS)	2015	65 (AS), 66 (RT), 70 (RP)

Table 3 (*Continued*)

#	Author	Year	Reference	Design	*N* or Response rate (%)	Country	Study population/ setting	Data collection method (instrument)	Study period	Age (mean)
24	Loeb et al	2015	[29]	Retrospective cohort/registry study	11 726	Sweden	Population database	Database	2003–2007	64
25	Lang et al	2017	[31]	Prospective survey to AS patients	531	USA	Clinical/hospital	Survey	2011–2012	Unknown
26	Hamdy et al	2016	[30]	Prospective cohort/registry study	1643	UK	Clinical/hospital	Survey/database	1999–2009	61
27	Kendel et al	2016	[79]	Prospective survey study—men on AS and RP	316	Germany	Clinical/hospital	Survey	2008–2013	67
28	Vasarainen et al	2012	[65]	Prospective cohort/registry study. HRQoL + drop-out	75 124	Helsinki	Clinical/hospital	Survey (RAND-36, IIEF-5, IPSS)	2006–2010	64
29	Bellardita et al	2013	[60]	Prospective cohort/registry study. HRQoL and database AS adjustment analysis	103	Italy	Clinical/hospital	Survey/database (mental health—symptom checklist-90, HRQoL—prostate version)	2007–2012	67
30	Vanagas et al	2013	[66]	Prospective survey study. HRQoL, anxiety, and depression among AS, RP, RT, chemo, and HT	61/650	Lithuania	Clinical/hospital	Survey (EORTC, QLQ-C30)	2010–2011	>64
31	Hegarty et al	2008	[61]	Retrospective survey of men on AS—to assess differences in HRQoL and anxiety and depression in men in the USA and Ireland	29	USA and Ireland	Clinical/hospital	Survey (MUIS-C, UCLA-PCI, QLI)	Unknown	76
32	Smith et al	2009	[70]	Retrospective cohort registry survey assessing AS HRQoL and cancer-related data 3 yr into an AS pathway	200/1647	Australia	Clinical/hospital	Survey/database (SF-12, IPSS)	2000–2002	63
33	Parker et al	2016	[63]	Prospective cohort survey assessing HRQoL and anxiety in AS	180	USA	Clinical/hospital	Survey (EPIC, SF-12)	2006–2012	67
34	Punnen et al	2013	[14]	Prospective cohort survey, assessing differences between RP and AS (at 1 and 3 yr) in respect to HRQoL, anxiety, and depression.	122/679	USA	Clinical/hospital	Survey (PHQ-9, GAD-7)	2007–2010	60
35	Lane et al	2016	[75]	Prospective cohort survey study, assessing HRQoL in AS, RP, RT	1438	UK	Clinical/hospital	Survey	1999–2009	61
36	van den Bergh et al	2010	[71]	Prospective cohort survey study (PRIAS) assessing progression, HRQoL, anxiety, depression, and patient factors between men on AS, RP, and RT	129/150	The Netherlands	Clinical/hospital	Survey (CES-D, STAI, SF-12)	2007–2008	65
37	Xu et al	2011	[81]	Qualitative interviews with patients with LRPC	7 black men, 14 white men	USA	Clinical/hospital	Qualitative interview (thematically analysed)	Unknown	Unknown
38	Xu et al	2016	[78]	Retrospective cross-sectional survey	266/391 (68%)	USA	Clinical/hospital	Survey	2009–2010	75
39	Wilcox et al	2014	[62]	Prospective survey of men on AS—assessing HRQoL, anxiety, and depression	47/61	Australia	Clinical/hospital	Survey (IIEF-5, IPSS, MAX-PC, UAS)	2013	62
40	Burnet et al	2007	[72]	Prospective survey study assessing anxiety and depression in men on AS	100/329	UK	Clinical/hospital	Survey (HADS)	Unknown	67
41	Davison and Goldenberg	2011	[73]	Retrospective survey study to assess the support and information men require to sustain them while on AS	25	Canada	Clinical/hospital	Survey (the control preference scale)	2009–2010	64
42	Anderson et al	2014	[74]	Prospective cohort survey study to assess anxieties in men with AS and determine which of these anxieties predicted HRQoL	86	Australia	Clinical/hospital	Survey (HADS MAX-PC, FACT-P, STAI)	Unknown	66
43	Oliffe et al	2009	[59]	A prospective survey study to describe the range of men's self-management strategies used to overcome AS-related uncertainty	25	Canada	Clinical/hospital	Survey	Unknown	Unknown
44	Berger et al	2014	[85]	Retrospective interview study to generate hypotheses about the factors that influence patients' decisions to leave AS	14/1159	USA	Clinical/hospital	Qualitative interviews (thematically analysed)	2010–2013	Unknown
45	Seiler et al	2012	[86]	Prospective cross-sectional survey study, to assess differences in anxiety and depression among couples	133	USA	Clinical/hospital	Survey	February 2010–August 2010	66
46	Kinsella et al	2015	[88]	Prospective education intervention to men on AS	117/244	UK	Clinical/hospital	Survey/database	2011–2012	63

Table 3 (*Continued*)

#	Author	Year	Reference	Design	*N* or Response rate (%)	Country	Study population/ setting	Data collection method (instrument)	Study period	Age (mean)
47	Bokhorst et al	2015	[93]	Retrospective registry study to determine the number of noncompliers with the follow-up protocol of the (PRIAS) study	4547	The Netherlands	Population database	Database/registry	Unknown	66
48	Wade et al	2015	[48]	A prospective cohort survey study assessing nurse-led AS clinics for accessibility, flexibility, and level of support	85	UK	Clinical/hospital	Survey and interviews (thematically analysed)	2006–2008	64
49	Weerakoon et al	2015	[12]	Retrospective registry study	1603	Australia	Population	Registry	2008–2012	66
50	Kazer et al	2011	[55]	Focus group analysis of the needs of men on AS	7	USA	Research	Focus group	2009–2010	70
51	Wade et al	2013	[49]	Prospective/retrospective survey study	1144 (88–95%) at 7 and 35 d after biopsy	UK	Clinical/research	Survey (HRQoL, HADS)	2006–2008	62
52	Wade et al	2015	[89]	In-depth semistructured interviews at 10 and 18 wk after biopsy	85	UK	Clinical/research	Interviews (thematically analysed)	2006–2008	64
53	Latini et al	2007	[80]	Retrospective survey study	105	USA	Registry/database	Survey (5-item fear of cancer reoccurrence questionnaire)	1997–2002	75
54	Jeldres et al	2015	[64]	A prospective cohort survey using validated HRQoL questionnaires	305	USA	Clinical/hospital	Survey (EPIC, RAND medical outcomes short form, SF-36)	2007	65 (AS), 58 (RP)
55	Donovan et al	2016	[68]	A prospective cohort survey using validated questionnaires to assess PROMs – HRQoL to compare men choosing surgery versus radiotherapy versus active monitoring	545/1643	UK	Clinical/hospital	Survey (EPIC, SF-12, HADS, EORTC, QLQ-C3021, ICQ-16, ICSmaleSF)	1999–2009	61
56	Parikh et al	2017	[36]	Retrospective cohort/registry study using the National Cancer Database to determine patterns of AS uptake	40 839	USA	Clinical/hospital	Registry	2010–2013	61 (CI), 63 (AS)
57	Loeb et al	2017	[83]	A qualitative study with patient focus groups and semistructured interviews with providers, to understand the informational needs of men on AS and influences on provider decision making	61	USA	Clinical/hospital	7 focus groups and 24 semistructured interviews	July 2015–March 2016	Unknown
58	Bokhorst et al	2016	[92]	A retrospective cohort review of hospital charts to assess the impact of biopsy complications on rebiopsy	1164	Worldwide	Clinical/hospital	Review of hospital charts	Unknown	Unknown
59	Le et al	2016	[43]	In-depth close-ended questions and semistructured telephone interviews, to assess decision-making processes by men and their partners in respect to AS and CI	30	USA	Clinical/hospital	Interviews	May–August 2011	Range 49–72
60	Scherr et al	2017	[53]	A retrospective review of hospital charts, structured interview questions, prospective Likert scale survey, and HRQoL-validated tools	92/211	USA	Clinical/hospital	Review of hospital charts, structured interview, survey (MAX-PC)	2008–2012	63
61	Taylor et al	2016	[28]	A prospective longitudinal cohort study of telephone interviews before treatment to assess influences on treatment decision preferences	1140	USA	Clinical/hospital	Interviews	2012–2014	61.5
62	Mader et al	2017	[42]	Retrospective patient semistructured interviews assessing choice factors in AS	15	USA	Clinical/hospital	Interviews	Unknown	65
63	Lyons et al	2017	[56]	A retrospective interview study on cognitive and affective processing involved in treatment decision making with patients and clinicians	18 providers and 19 patients	USA	Clinical/hospital	Interviews	Unknown	65
64	Chen et al	2017	[69]	A prospective cohort survey using a validated questionnaire to assess HRQoL	314/1141	USA	Clinical/hospital	Survey (prostate cancer symptom indices)	2011–2013	67

AS = active surveillance; HRQoL = health-related quality of life; HT = hormone therapy; IPSS = International Prostate Symptom Score; LRPC = low-risk prostate cancer; NA = not available; PC = prostate cancer; PRIAS = Prostate Cancer Research International: Active Surveillance; RP = radical prostatectomy; RT = radiotherapy; UCLA-PCI = University of California, Los Angeles, Prostate Cancer Index.

content analysis, one intervention study, and seven mixed-method studies. Seventeen studies reported HRQoL and/or psychological assessment data using validated questionnaires/tools (Supplementary material, Validated tools).

Some overlap in studies was noted with eight of 64 studies reporting on factors influencing both AS choice and adherence.

3.2. Results

This review has been split into two sections: barriers and facilitators to AS selection and to AS adherence. These have further been synthesised and these demonstrate influence on six different levels: cancer characteristics, patient factors, family and social support, provider, organisation and practice, and health policy. The sections below discuss facilitators and barriers according to these levels.

3.2.1. Barriers and facilitators to AS selection

3.2.1.1. Cancer characteristics

3.2.1.1.1. Facilitators. Nine studies described how cancer characteristics such as PSA, number of positive cores, Gleason score, and tumour volume influenced the selection of patients for AS. A low Gleason score and a low PSA value were identified as facilitators of AS in five of these studies [11,22–25]. Five studies [22,23,26–28] also suggested that tumour volume played an influential role in AS selection, with lower volume associated with higher levels of AS selection.

3.2.1.1.2. Barriers. The UK-based Prostate Testing for Cancer and Treatment (ProtecT) study, USA-based CEASAR study, and Swedish NPCR [29–31] found that men with higher PSAs and tumour staging were disinclined to choose AS when diagnosed.

3.2.1.2. Patient level

3.2.1.2.1. Facilitators. Seven studies [26,28,32–36] indicated that older men were more likely to choose AS than younger men, but were in general less engaged in the decision-making process than younger men [32]. Comorbidity was featured in seven studies [11,22,24,33–35,37]. The Surveillance, Epidemiology and End Results (SEER) registry reviews [34,37], the US National Cancer Database (NCDB) [34], Swedish studies [11,24], a US multidisciplinary clinic study [22] based in Boston, and the Michigan MUSIC study [23] showed an association between a higher Charlson comorbidity index and choice of AS. Orom et al [33], however, found that the presence of cardiovascular disease was associated with a greater likelihood of choosing radiation over AS. Both Orom et al's [39] and Parikh et al's [36] studies suggested that men with more years of education were more willing to opt for AS; however, another study suggested that higher education was a barrier to AS choice [24].

Six studies [25,32,40–43] suggested that fear of side effects (in particular, erectile dysfunction and incontinence) following radical treatment was a strong determinant of AS. Ehdaie et al [44] found that significantly more men opted for AS (12%) if during treatment counselling they had proactively been encouraged not to ignore potential harms of treatment.

3.2.1.2.2. Barriers. Nine studies showed that younger men were less likely to choose AS. Three studies [32,33,45] found that men younger than 60 yr were less likely to choose AS. One comment from a patient in a qualitative interview was "choosing AS would be irresponsible, ridiculous even at my age (aged 53)".

Other studies reported patient-related factors including ethnicity and family history of PC. Aizer et al [22] suggested that family history of PC increased the likelihood of early dropout from AS; this is consistent with Volk et al's [40] interview findings that twice as many patients who opted for primary curative treatment had a relative with PC, compared with patients who opted for AS. Xu et al's [27] study showed that black men, as compared with white, were less likely to choose radical treatment and specifically surgery, due to the high risk of adverse effects. In contrast, Orom et al's [33] survey suggested a racial difference in the use of AS, with a higher proportion of black men choosing radiotherapy over AS.

The association between the level of education and AS is inconsistent: the Prostate Cancer Database Sweden (PCBaSe) [24] suggested that a higher level of education precipitates lower use of AS in the LRPC group (26% of men vs 39% with a midlevel education and 35% with a lower education level).

The psychological burden of AS with respect to the associated repeat testing during AS [46,47], as well as the morbidity from repeat prostate biopsies [25], was also linked to reduced uptake of AS. Wade et al [48,49] found that men who were well informed about prostate biopsy were less likely to refuse repeat biopsy. This is important to acknowledge in the context of AS where monitoring includes regular rebiopsy. However, several studies have described the process of repeat testing on AS as a reassuring process [40,42,46].

3.2.1.3. Family and social support

3.2.1.3.1. Facilitators. In all the interview studies, men on AS described justifying their decision to others as one of the most difficult aspects of the decision-making process. Both Xu et al [45] and Goh et al [50] reported that AS referred to as "no treatment" was often more challenging for the spouse and children to understand than for the patient. Successful reassurance and education of the family were highlighted as key facilitators to patients choosing and adhering to AS [40,45,46].

Four interview studies from the USA, UK, and Canada [25,32,40,46] showed that "avoidance of treatment side effects", "more convenient for lifestyle", and a "combination of reasons" were recurring themes explaining the choice of AS. The UK study [25] also showed that men were as satisfied with their decision to undertake AS as those who had undergone radical treatment 2 yr later.

3.2.1.3.2. Barriers. Pressure from family and friends has been found to be high at the point of diagnosis, many of whom urged curative treatment [45,47]. To give an example, in qualitative interviews performed by Xu et al [45], one man stated that he initially preferred AS plus nutrition supplements to avoid treatment-related side effects, but that his family pressured him to choose radical prostatectomy (RP), and as a compromise, he finally chose radiation. In another example, one man stated that he felt unspoken pressure from his family to choose curative treatment.

Perception and acceptance of AS requires careful management. Orom et al's [33] 2017 survey described that high levels of distress at the time of diagnosis and at the time of the treatment decision were predictors for choosing RP over AS. In contrast, Xu et al [27] found that black men were more likely to report higher levels of "cancer worry", but that their perception of the negative effects of radical treatment often led to fewer men choosing radical treatment.

3.2.1.4. Healthcare provider level

3.2.1.4.1. Facilitators. Eleven of the reviewed studies suggested that the clinician heavily influences the decision-making process [26,32,33,41,44,46,47,50–53]. Scherr et al [53], Liu et al [26], and Davison and Breckon [32] all found that the diagnosing urologist was the most influential clinician associated with AS choice. Orom et al's [51] 2014 survey found that a poor relationship between patient and clinician was mentioned by only 1% of men who were appropriately recommended AS for LRPC, but by as many as 53% of men who were recommended a definitive treatment only.

Loeb et al [52] found that clinicians were concerned about the burden of intensive monitoring and that they might miss disease progression. However, both Orom et al [51] and Loeb et al [52] found that shared decision making would address this.

Health literacy is defined as an "individual's capacity to access, understand, communicate, evaluate, utilise, and make decisions based on health information" [54]. Therefore, provision and access to relevant information are a consistent theme in both increasing the uptake of and adherence to AS. Mishra et al [47] described the views of patients and their families in Internet conversations over a 10-yr period; they found that access to unbiased information was associated with more patients opting for AS. Four other studies [32,40,42,46] reported similar results. Goh et al [50] found that men who perceived that they were receiving consistent information felt more in control of their decision making, and experienced a greater degree of satisfaction and certainty in choosing AS. Three other studies concluded that access to educational resources, in addition to professional and peer support (supported self-management), optimised the treatment selection process and empowered men "to take control" of their diagnosis and their choices thereafter [42,47,55]. However, in contrast, Taylor and colleagues [28] found that even when patients had access to information and support, men who choose AS were less likely to access these resources than those choosing radical treatment.

A US multidisciplinary clinic study [22] found that AS selection was further facilitated through a multidisciplinary provider approach, removing the bias of treatment recommendation, which is often associated with clinicians who carry out a particular treatment. Patients receiving treatment counselling from two or more specialist clinicians were twice as likely to opt for AS than radical treatment (43% vs 22%). This was further confirmed and described during semistructured interviews by Lyons et al [56].

Ehdaie et al [44] further found that a systematic approach for communicating the merits of AS using appropriate framing techniques increased the proportion of patients selecting AS (69% before intervention to 81% afterwards), equating to a 30% relative reduction in unnecessary curative treatment.

Several studies have also reported that by slowing down the treatment decision-making process, providers might influence an increase in the proportion of men choosing AS [46,47,56]. Volk and colleagues [40] found significance in men viewing their cancer as "low risk" as it offered an opportunity to postpone treatment, allowing sufficient time for technological advances in treatment. Based on their answer to the question whether men chose AS as a holding mechanism only or as a long-term solution, patients were fitted into two groups: those who concluded that selection of AS meant avoidance of side effects and those who felt that AS gave them time to make a treatment decision.

3.2.1.4.2. Barriers. Conversely, the clinician's influence has also been listed as a barrier for choice of AS. Mishra et al's [47] review of the changing trends in Internet conversations over a 10-yr period suggested that patients were increasingly receptive to considering AS, but many questioned if physicians could provide an unbiased treatment recommendation. This concern was also articulated in four of the interview studies [40,45,46,50] where patients expressed concern about the possibility of clinician bias at the time of consultation, with many of them recalling that either they were not offered AS as an option or the patient perception of AS was "doing nothing". Scherr and colleagues [53] reviewed patient-physician interactions over the period that treatment decisions were made and found that physicians were heavily influenced by age and Gleason score, but not by the value that patients put on treatment outcomes, for example, sexual dysfunction.

Parikh and colleagues [36] used the NCDB to review 40 839 men with LRPC in relation to a number of variables. They found that the barriers to AS included living a longer distance from the provider facility, and those men were diagnosed by a physician working outside of an academic or research facility.

3.2.1.5. Healthcare organisation and practice level

3.2.1.5.1. Facilitators and barriers. Many narrative reviews of AS highlight differences in AS protocols among healthcare providers and healthcare systems, and also within

individual countries [11,12,23,26]. For example, the MUSIC group found that the use of AS varied substantially between different urology practices in the state of Michigan, ranging from 27% to 80% of eligible patients [23,26]. This variability could simply be attributed to the recommendation of the clinician, but two studies [40,47] focused on access to clinical expertise and technology, suggesting that patients felt that they were offered AS only when there was availability of imaging facilities and expert clinicians to deliver the AS protocol. A similar diagnostic practice–related influence was also observed in the Michigan MUSIC study [23,26].

Type of healthcare system as a barrier to AS was mentioned in one study [52], which found that the US system placed limitations on a clinician's ability to recommend AS (although did not find that this was due to financial incentives) and carry out the necessary regular retesting associated with AS. However, Parikh and colleagues [36] found that analysis of the NCDB suggested higher uptake of AS in the uninsured.

3.2.1.6. Health policy level

3.2.1.6.1. Facilitators and barriers. In 2006–2007, Mishra et al [47] reported that patient and clinician attitudes towards AS (calculated numerically as a "sentiment index" in the content in Internet conversations) were at their lowest, with both judging AS "not safe" and "should only be offered to older patients". By 2009, Mishra et al found the Internet sentiment index was high, meaning that there was a more positive attitude towards AS. Reasons for this included a 2009 American Urology Association endorsement for AS [57] and a 2010 publication of a large-scale AS cohort [58] reporting a very low mortality rate over intermediate follow-up. In Sweden, Loeb and colleagues [11] also found that AS uptake (2009–2014) significantly increased and hypothesised that this was largely due to national guidelines recommending AS.

3.2.2. Barriers and facilitators to AS adherence

3.2.2.1. Cancer characteristics

3.2.2.1.1. Facilitators. Several population-based studies reported on cancer characteristics in relation to AS adherence. The UK-based study, US-based CEASAR study, and Swedish NPCR [29–31] found that men with lower PSAs and tumour staging were more inclined to adhere to AS.

3.2.2.1.2. Barriers. The Swedish NPCR study [29] reported that the <65-yr age group and those with higher education levels (<9 yr full-time education) were significantly less likely to continue AS than the older and less educated groups. These findings have been replicated in qualitative studies such as those carried out by Lang et al [31] and O'Callaghan et al [46], which found that younger men with a higher educational level found the notion of long-term AS, that is, "doing nothing", less tolerable than the associated morbidity of radical treatment. The Swedish NPCR study [29] also reported that out of those men who discontinued AS, 52% did so because of PSA progression and 24% due to biopsy progression.

3.2.2.2. Patient level

3.2.2.2.1. Facilitators. Patient-perceived experience of AS featured in three studies. Goh et al [50] analysed the experience of AS in 34 men, and found that those who viewed their experience with cancer as having a positive impact on their lives were better able to manage the uncertainty of AS and felt more in control of their decision making and during AS. Oliffe et al [59] found that men reporting a higher level of positivity in the face of their cancer diagnosis (attributed to consistency in information and support) were less likely to exhibit decision-making conflict related to the perceived effectiveness of their treatment plan and may therefore be more inclined to remain on AS. These studies suggest that careful patient selection is important for both treatment choice and adherence [50,59]. Volk et al [40] found that men described the process of AS as an organised, supportive process of regular monitoring.

Four of the seven HRQoL studies had no control group [60–63]. Wilcox et al [62] and Jeldres et al [64] found no change in HRQoL before or after entry into an AS programme. Parker et al [63] found that as age and body mass index increased, HRQoL decreased over time. Both Parker et al [63] and Bellardita et al [60] found that HRQoL improved >5 mo after diagnosis and commencement of AS.

Bellardita et al [60] also noted that men with a partner and men who had >18 biopsy cores taken at diagnosis were more likely to have good HRQoL on AS. Hegarty et al [61] compared HRQoL between men on AS in Ireland and the USA: general HRQoL and vitality were lower in the US group—which they reported was likely due to differences in healthcare expectations.

The six studies that included control individuals of either men with no cancer [65] or those undergoing radical treatment [66–69] or both [70] showed no statistical differences in HRQoL between the control individuals and men on AS. The Finnish section of the Prostate Cancer Research International: Active Surveillance (PRIAS) study [65] found better than average HRQoL (as defined by the RAND-36 questionnaire) than in the general Finnish male population, both immediately following entry into AS and 1 yr later. Both Vanagas et al [66] and Venderbos et al [67] reported better HRQoL in men on AS than in men who had undergone radical treatment with respect to physical, emotional, and social scales. Donovan and colleagues [68] reviewed patient-reported outcomes comparing monitoring with surgery and radiotherapy as part of the ProtecT trial. The monitoring cohort consistently did better with respect to three of the four domains: erectile, urinary, and bowel function; however, there was no significant difference in HRQoL among the three treatment groups. Smith et al [70] found similar HRQoL scores across AS and treatment groups. Chen and colleagues [69] reported similar results recently from the North Carolina Prostate Cancer Comparative Effectiveness and Survivorship Study where contemporary PC treatments were compared with AS in respect of HRQoL. However, after 24 mo it was notable

that QoL scores were not clinically meaningfully different between the treatment and AS groups.

When measuring the anxiety associated with long-term surveillance adherence, the majority of studies included in this review suggested that anxiety reduced [65,66] or remained the same over time [14,60,62,71–74], with no observed impact on long-term adherence.

In the recently published ProtecT study, depression was reported in only 6% of the 545 men allocated to active monitoring over a period of 10 yr, suggesting that depression and anxiety do not increase significantly while on AS [30,75].

A number of studies have shown that emotional distress is relatively high in men at the time of their PC diagnosis [33,76]. However, anxiety in men on long-term AS has generally been reported as favourably low. A 2015 systematic review [77] reported no overall difference between levels of anxiety following diagnosis of LRPC and during AS, which was reported as between 4% and 15%. In fact, more studies have suggested that anxiety in men on AS reduces [65,66,71] or remains the same over time [14,60,62,71–74].

3.2.2.2.2. Barriers. The Swedish NPCR study [29] reported that out of those men who discontinued AS, 20% stopped due to patient preference alone. The US-based CEASAR study [31], which included men from five SEER catchment areas, and the CaPSURE database [31] found that 8–23% of men converted to curative treatment for reasons of personal preference rather than disease progression.

These findings were further explored in two large qualitative studies exploring men's survival expectations as a result of selecting treatment for LRPC. Xu et al [78] reviewed men's perceptions of the likely benefits and harms of radical treatment versus no treatment (AS). This was calculated in the form of patient-perceived life expectancy (LE). At the time of the survey, two-thirds of the 229 men had started or completed treatment. Of these, 30% in the AS group expected to live <5 yr. This was in contrast to that in the treatment group where >95% of patients estimated their LE to be >5 yr. Kendel et al [79] also reviewed perceptions of the risk of death from PC between matched patients who had undergone AS or RP. Men who had undergone RP estimated the risk of dying from PC associated with AS to an average of 51%, at least a 10-fold overestimation of the true risk. They believed that their 10-yr risk of dying from PC after RP was only one-third of the risk of AS (18%— also a substantial overestimation). Both studies thus suggest that patients' perception of survival is a barrier to both AS selection and long-term adherence.

Although some studies suggested that "fear of cancer progression" may be a limiting factor to choosing AS [59,80–82], none have convincingly shown that this contributes to a significant number of men opting out of AS without documented clinical progression (Venderbos et al [82] found that this was 5%). Both Davison and Goldenberg [73] and Parker et al [63] found that the degree of "fear of progression" did not change significantly over a period of AS.

3.2.2.3. Family and social support

3.2.2.3.1. Facilitators. Four studies highlighted that successful reassurance and education of the family was a key facilitator to patients both in choosing and adhering to AS [40,45,46]. Loeb et al's [83] qualitative focus group and interview study found that social support and interaction (support groups, online forums, support for spouse, and family) were of particular importance in AS adherence. An AS support group for both family and men with PC was a particularly strong recommendation. Mader et al [42] interviewed 15 men following their decision for AS, and found a strong correlation between AS adherence and social support, including spouse, extended family, and experiences of others. Anandadas and colleagues [25] further demonstrated that men were equally as satisfied with their decision to undertake AS as those who had undergone radical treatment 2 yr later.

3.2.2.3.2. Barriers. Pressure from family and friends is reportedly high at the point of diagnosis, many of whom urge curative treatment [45,47]. The experiences of friends and family members with cancer (often not PC) are consistently reported as a significant pressure in men on AS [45,47]. Berger et al [85] noted that men reported leaving AS and pursuing treatment to limit their loved ones' worry, or in reaction to the fear of cancer expressed by their family. Partner anxiety was also documented by Seiler et al [86], who compared levels of anxiety and depression between men on AS and their partners. Anxiety scores were much lower in the men than in their partners. The CaPSURE database [31] found that 16% of men converted to curative treatment on the basis of "spousal encouragement".

3.2.2.4. Healthcare provider

3.2.2.4.1. Facilitators. Seven studies identified facilitators to AS adherence, including education, self-management techniques, healthcare professional, and peer support in the furtherance of increasing AS adherence. Loeb et al's [83] combination of focus groups and semistructured interviews found six themes relating to the facilitation of AS adherence. Five of these were consistent with healthcare provider responsibilities in the form of informational needs: (1) information on PC (biopsy features and prognosis); (2) information on AS (testing protocol, and difference between AS and WW); (3) information on complimentary options (diet and lifestyle); (4) variety of resources (source and format); and (5) integrity of information (trusted source, secure, and multidisciplinary). Oliffe et al [59] found that self-management strategies helped men cope with some of the long-term uncertainties of AS, while "the Prostate Cancer Lifestyle Trial" based on lifestyle modifications, including exercise and attention to stress management, demonstrated improved treatment-free survival for men on AS [87]. Goh et al [50] found that men who perceived that they were receiving useful consistent information were more satisfied with AS and therefore more likely to continue on AS. Kinsella and colleagues [88] found that AS classes

significantly improved long-term adherence to AS, as did consistency of personnel to support and inform patients, as found in the UK-based ProtecT trial [89]. Interventions relating to peer support have also demonstrated a significant improvement in the quality of life of men with any stage of PC [88,89].

3.2.2.4.2. Barriers. The ability of healthcare providers to deliver long-term support to patients on AS was highlighted in several studies [85,90,91]. Men leaving AS describe a number of unmet supportive care needs [85]. These include lack of education and clarity concerning the correct time to pursue treatment, and triggers for treatment from both patient and relative perspective.

Two studies [90,91] specifically focused on the influence of support groups. These noted either no effect or even a negative effect on long-term AS adherence, possibly due to the group consisting of a mix of survivors, that is, those who had undergone radical treatment and those on AS [91]. Chapple et al [90] found that support groups were of no help to men on AS, with one man reporting that he felt he "had to defend himself" in the support group for choosing AS.

Mishra et al [47] concluded that there was a lack of availability of consistent and reliable information to men during long-term AS.

3.2.2.5. Healthcare organisation and practice level

3.2.2.5.1. Facilitators and barriers. Differences in surveillance strategies have also demonstrated an association with adherence in both a positive and a negative respect (Supplementary material, Overview of large cohort active surveillance studies). These contemporary cohort studies all include a strategy of repeat biopsy as part of a robust AS protocol. Two studies found that prostate biopsy was associated with significant morbidity, and AS adherence could therefore be influenced by frequency/requirement to rebiopsy. The ProBE (The effects of prostate biopsy) study nested within ProtecT assessed patient response to prostate biopsy and indicated that 25% of men who had undergone prostate biopsy were disinclined to undergo subsequent biopsies [48], while a study by Bokhorst et al [92] as part of the PRIAS study suggested that complications following prostate biopsy were not uncommon (20% of men), and after complications men were less likely to accept repeat biopsy.

However, in two interview-based studies that took place in the USA [40,46], men gave a consistent description of AS, viewing it as a reassuring, organised, and supportive process despite invasive testing.

3.2.2.6. Health policy level

3.2.2.6.1. Facilitators and barriers. AS protocols with respect to patient selection, safe monitoring, and triggers for intervention vary between study cohorts, healthcare systems, and countries, which makes it difficult to produce a coherent, consistent clinical guidance document. In Sweden, Loeb and colleagues [11] found that AS uptake and adherence (2009–2014) significantly increased and hypothesised that this was largely due to clear national guidelines recommending AS. Likewise, the PRIAS study [93] suggested improved compliance and adherence as part of an official AS programme.

3.2.3. Result synthesis

The barriers and facilitators to AS choice and adherence were categorised into six levels as part of this review: cancer characteristics, patient, family and social support, provider, healthcare organisation and practice, and health policy; these are summarised in Table 4. These barriers and facilitators varied in both strength of association and level of evidence, and are described in Figure 3. The barriers and facilitators identified as most influential over the six levels are symbolised as circles, with larger circles representing a greater degree of evidence as supported by this review.

3.3. Discussion

A demonstrable rise in the use of AS has been noted over a short time frame; however, there are significant differences between individual healthcare providers as seen in the US CaPSURE database [5] and Swedish PCBaSe [11]. Local guidelines, national policy, patient education, supportive care, and medicolegal factors may be important factors driving this variation [10,12], and therefore, these issues require greater consideration and management if we are to better facilitate AS.

Studies focusing on men's perception of risk as a barrier to choosing AS show that men continue to grossly overestimate the risk of dying from LRPC while on AS [25,32,45,47]. Moreover, understanding the implications of HRQoL and psychological factors on the decision to both choose and adhere to AS requires further multidimensional assessment and interpretation. Clinicians and patient groups actively encourage the increasing responsibility that PC patients are taking for self-directed management and informed decision making [87,94]. Such patient empowerment has positive psychological effects on cancer patients in general and should be explored in the specific context of AS [87,94].

These elements have been explored in the context of the chronic disease setting, which one could argue relates well to a diagnosis of LRPC that may never require curative treatment. A systematic review of general health screening and treatment decision making in the chronic disease setting [95] found that clinicians employing a process of "motivational interviewing" consistently improved patients' knowledge, perception of risk, and increased confidence in decision making. Motivational interviewing is specifically designed to help patients identify and resolve ambivalence about changing their behaviour by exploring personal perspectives and perceived barriers [96]. It employs a four-step guiding style (engaging, focusing, evoking, and planning) to foster a constructive clinician-patient relationship. Joosten et al [97] found that motivational interviewing improved the patients' ability to self-manage and increased adherence to chronic disease management plans.

Table 4 – Summary table of determinants of choice and adherence to active surveillance among men with low-risk prostate cancer found in the systematic review

Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
1. Cancer characteristics	Cancer risk, stage, grade, PSA, tumour volume	Harmonising national/local guidelines; developing consensus-based appropriateness criteria	[11,22–31]
2. Patient	Shared or collaborative role in decision making; preferences; seeking information; feeling informed; knowledge	Shared decision making; appropriate, reliable, and unbiased information; personal information; not contradictory and not stressful; increased availability of educational resources from trusted medical organisations for patients and families	[27,32,41,46,50]
	Patient characteristics (age, comorbidities, race, family history of prostate cancer, education, employment, insurance, socioeconomic status)	Physician judgement and recommendation in shared decision making with patient preference	[11,12,22–29,31–37, 40,46,68]
	Impact of active treatment on side effects (urinary function, sexual function); preservation of HRQoL; time to accept diagnosis and to decide; "buying time"	Patient education and information. Proactive self-management strategies for post-treatment side effects	[25,27,28,32,40–43,46, 47,53,60–62,64–67, 69,70,75]
	Self-management support; preference style for diet, exercise and complimentary therapies; increased awareness and control of health; hope for prolonged and improved health; symptom monitoring; lifestyle	Patient education and information; self-management through diet and exercise, stress management, digital technology	[25,32,40,46,50,83]
	Preference for immediate cure; "cut it out"; desiring treatment efficacy/cure; avoid future regret	Patient education and information; supportive counselling	[27,31,40,43,45,80]
	Perceived cancer risk; cancer worry; fear of disease progression; illness uncertainty; anxiety and distress	Patient education and information; support; coping; manage anxiety; cognitive reframing; mindfulness; meditation; empowering; support groups; peer community; socialisation; connect to others; shared activities; sense of belonging; providing patients with a sense of meaning and control, robust monitoring processes, widespread agreement on monitoring process	[14,25,27,30,32,33,40,41, 44–46,50,53,59,60,62, 63,65,66,71,72,74, 78–82,86]
	Monitoring stressors; coping with anxiety, frequent PSA testing, and repeat biopsies	Patient education and information; support; coping; development of noninvasive monitoring	[25,27,32,40, 46–48,60,92,93]
	Awareness and acceptance of AS; survival expectation on AS	Availability of AS "success stories"	[47,50,59,73,78]
	Unknown factors	Qualitative interview studies with physicians and patients	[40,45,46,52]
3. Family and social support	Advice/pressure from partner/spouse/children/ friends; marital status; family member with PC	Supportive counselling and information; patient not having to justify decision to others; support; education; reassurance	[32,40–42,45,46,62,85]
	Awareness and acceptance of AS	Public role models managed with AS and patient advocates	[40,42,45–47,85,86]
	Fear of progression; disagreement about safety; preference to "eradicate the cancer"	Counselling and information; enhanced recognition with information sources, treatment support, medical consultations	[45–47,50]
4. Provider	Physician's recommendation; consistency in medical/nursing personnel	Training specialists to use a systematic approach to counselling patients about treatment options; communicating clearly and with confidence; using nudging narratives and framing techniques from behavioural science theory; maintaining a positive and hopeful attitude; providing support and reassurance; public reporting of physicians' cancer management profiles	[26,30,32–34,40–42, 44–47,50,52,53,89]
	Speciality of physician giving treatment information	Multidisciplinary team of specialists	[22,26,32,56]
	Provision of information and support	Providing and directing patients to accurate and unbiased information rather than describing AS as "doing nothing" or "no treatment" or scaring patients to active treatment, access to AS support groups. Establishing consistency of support through nurse specialist roles. Promotion of social support networks. Access to decisional aids	[26,28,32,40,43,46, 47,50,55,56,59,83,88,89]
	Physician attitudes; reluctance; concern about disease progression; perceived lack of data	Raise awareness, ongoing discussions at national meetings, quality improvement initiatives; having clear plans and stopping rules; systematic counselling on AS	[40,44–47,51,52]
	Lack of availability of physicians recommending AS	Advocacy; subspecialty within urology	[40,47]
	Confidence and trust in health professionals; closeness with physician; share control over treatment decision making	Improved community and medical education about treatment options, prognosis, side effects; raise awareness of AS; consistent, unbiased treatment information; decisional support information; building trust in physician; patient trusting the physician's monitoring; patient feeling AS is an organised, supportive process	[40,46,51,52,89]

Table 4 (*Continued*)

Level	Factor	Potentially targetable interventions for future research and quality improvement initiatives	References
5. Healthcare organisation/ practice	Urology practice site; hospital referral region; geographic region	Quality improvement initiatives to harmonise practice sites within networks	[26,35–37,46,47]
	Degree to which physician shared control over treatment decision making	System-level determinants of trust, closeness, and shared decision making; organisational changes (eg, longer consultation times)	[40,51,52]
	Consultation at a multidisciplinary clinic; university hospital setting; academic hospital or high volume of PC patients	Multidisciplinary clinic may reduce the bias that specialists prefer the modality of treatment they themselves deliver and patients receive a balance perspective of risks and benefits of options	[11,22,24,35–37]
	Differences in surveillance strategies	National/international consensus of safe AS. Selection, monitoring and progression, patient information on large AS cohorts	[11,12,23,26,88,93]
6. Health policy level	Guideline recommendations	Harmonising national/local guidelines; developing appropriateness criteria; national guideline recommending AS; real-time feedback to units on adherence to national guideline in terms of annual report publicly available online	[11,47,52,53]
	Trial/cohort data; year of diagnosis	Monitoring and future publications from ongoing prospective protocol-based AS cohorts and registries	[11,35,47,52]
	Awareness and acceptance	Guidelines; consensus; discussions at meetings; AS-specific billing code	[47,52]

AS = active surveillance; HRQoL = health-related quality of life; PC = prostate cancer; PSA = prostate-specific antigen.

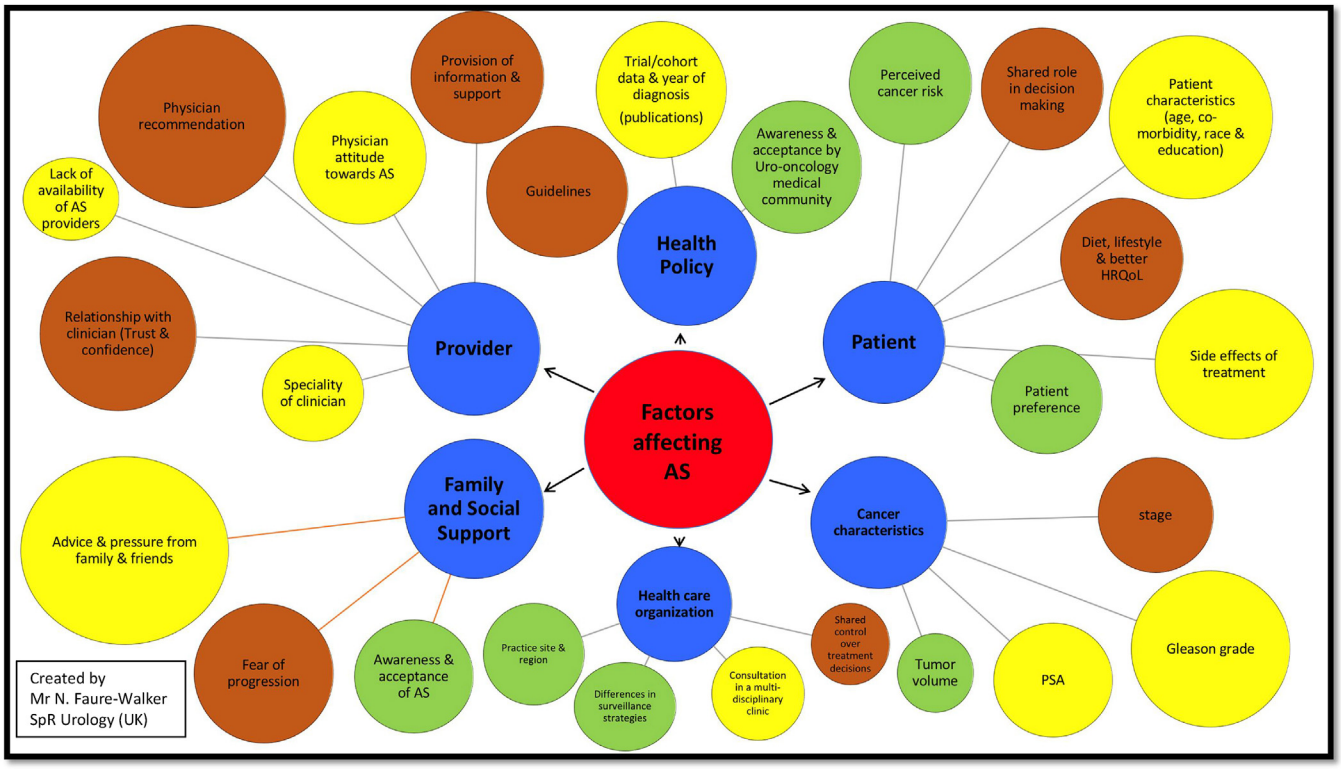

Fig. 3 – Barriers and facilitators to AS choice and adherence; size of circle signifies the strength of evidence for each influencing factor. Yellow circles indicate that the evidence is strongest for AS choice, green circles indicate that the evidence is strongest for AS adherence, and brown circles indicate that the evidence is relevant to both AS choice and AS adherence. AS = active surveillance; HRQoL = health-related quality of life; PSA = prostate-specific antigen.

Although there is currently no published experience of motivational interviewing in AS, a recent systematic review in other cancer patients [98] found that it was useful for eliciting lifestyle behavioural changes, decreasing cancer-related anxiety, and encouraging supported self-management. This also supports that argument that men on AS experience a similar physical and psychological burden to people living with other chronic conditions [99], such as asthma and diabetes [100–104], for whom quality of life relies on adherence to a treatment plan with the aim to optimise disease control, maintain quality of life, and prevent unnecessary escalation of treatment.

Another systematic review [100] outlining the merits of supportive self-management in chronic disease adherence suggested that there are core components of support and that their implementation requires a holistic approach, which intervenes at the level of the patient, the healthcare professional, and the organisation, much in the same way as identified in this review of AS:

1. Provision of education about the long-term condition (LTC)
2. Psychological strategies to support adjustment to the LTC
3. Practical support tailored to the LTC (eg, support around activities of daily living for disabling conditions and action plans in conditions subject to marked exacerbations)
4. Social support
5. Lifestyle modifications (eg, diet and exercise)

Our current systematic review highlights the need for improved validated methods for patient and physician education to facilitate the uptake of AS among men with LRPC. Moreover, studies suggesting that clinician's bias may influence the treatment decision-making process [26,32,33,41,46,47,50,51] suggest that educational efforts aimed at clinicians and frameworks for how they deliver the information on treatment options [44] are important for increasing the acceptance of AS. Education, appropriate information, and support aimed at both patients and their families have long been recognised as important in the management of chronic conditions [77,78], with studies demonstrating an increase in adherence to treatment plans where these have been established.

In addition, many chronic disease studies have successfully explored strategies to reduce healthcare inequalities in chronic health conditions [103,105,106]. This has been achieved through the standardisation of education and training to both clinicians and patients, development of educational materials and decision aids, as well as creation of specialist centres for chronic conditions. To date, one study has replicated this in the context of AS. Formica and colleagues [107] reported that decision aids in combination with standardised patient education packages achieved a three-fold increase in AS acceptance.

Several AS papers suggested that national guidelines could have a significant impact on selection and adherence to AS [11,47,93]. This has been replicated in the chronic disease setting [104,108]. In diabetes management, introduction of the Dutch guidelines increased clinician adherence by 60%, suggesting that guidelines are reassuring for both patients and clinicians [108]. The current discordance in AS management makes internationally ratified guidelines a priority, and efforts such as those employed by the GAP3 consortium (Movember) [109], which has established active communication and collaboration among research groups worldwide, are likely to change this. GAP3 aims to reach international consensus on the definitions and terms used in AS through analysis of a global database including >14 000 patients [109].

The requirement for continuous monitoring in AS has been described as both a barrier and a facilitator. In chronic disease management, it gave rise to early developments in telehealth with some studies suggesting that easy-to-learn applications can improve adherence, lessen disease impact, accelerate behaviour change to improve outcomes, and increase patient and partner confidence during remote monitoring [110,111]. AS monitoring protocols are currently undergoing rationalisation, with more frequent imaging and fewer biopsies. Although we found no reports of the use of mobile health applications in the AS setting and only one small pilot of an Internet-based application specifically aimed at managing uncertainty in AS [112], the change in the way we survey patients could lend itself to the introduction of robust remote monitoring using this technology.

The role of social media in choice and adherence to AS has not yet been explored; however, online social networks have changed the way we communicate and provide new ways to engage patients. Twitter and Facebook groups established to engage cancer patients offer easy access to peer support and have been associated with less stress, anxiety, and depression [86,87]; in the chronic disease setting, Kirwan et al [113] found that combining [114] online applications and social networking significantly increased diabetic glycaemic control in comparison with the control group.

A combination of these core elements is critical to ensuring positive experience and benefit of living with LRPC on AS.

Advances in PC management including the use of multiparametric MRI, and more sophisticated prostate biopsy strategies in both diagnostics and surveillance programmes could also change the level of reassurance in AS. Alongside this, a recent systematic review focused on the development of genomic profiling suggests that combining data of genome-wide association studies with gene expression and structural rearrangements and risk alleles could provide a new basis for developing a prognostication tool to guide therapy for men with LRPC [114].

3.4. Limitations

This review is limited as a mixed-methodology paper. The included studies were heterogeneous and therefore a meta-analysis was not possible. This type of systematic review relies on a reasonable number of included studies for strength; however, the weighting of individual studies needs to be adjusted based on the varying levels of evidence and methodological quality of the included studies. However, this has been represented using the PREFS quality checklist and a modified STROBE checklist, which was reviewed by the three reviewers independently.

Of the papers reviewed, some did not distinguish entirely between AS and WW, and therefore older age and comorbidity as facilitators to AS may be inaccurate in 2018. Another limitation concerns the generalisability. More than 50% of studies were North American, and this healthcare system may not be generalisable to other countries.

4. Conclusions

Many factors influence men's choice and adherence to AS, such as the clinician's attitudes, family and social support, and patient education. The clear recommendations of this review include agreed international guidelines on AS and the introduction of a multidisciplinary management strategy with psychological support to facilitate the AS. Current clinical practice at centres with high AS uptake may provide insight into the changes required to ultimately decrease the overtreatment of PC worldwide, while experience gathered in the chronic disease setting, such as the introduction of supportive self-management, social media interventions, and motivational interviewing, could form the blueprint for future AS programmes to increase both choice of and adherence to AS in LRPC.

Author contributions: Netty Kinsella had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Van Hemelrijck, Carlsson, Kinsella.
Acquisition of data: Van Hemelrijck, Carlsson, Kinsella.
Analysis and interpretation of data: Carlsson, Kinsella, Van Hemelrijck.
Drafting of the manuscript: Van Hemelrijck, Kinsella, Carlsson.
Critical revision of the manuscript for important intellectual content: Van Hemelrijck, Stattin, Bratt, Bill-Axelson, Brown, Cahill.
Statistical analysis: None.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Van Hemelrijck, Carlsson.
Other: None.

Financial disclosures: Netty Kinsella certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Sigrid Carlsson is supported in part by a Cancer Center Support Grant from the National Cancer Institute made to Memorial Sloan Kettering Cancer Center (P30-CA008748), a SPORE grant from the National Cancer Institute to Dr. H. Scher (P50-CA092629), a grant from the National Cancer Institute as part of the Cancer Intervention and Surveillance Modeling Network (U01CA199338-02) and the David H. Koch prostate cancer research fund. Ola Bratt is supported by the Swedish Cancer Foundation (2012/475). No author has any conflict of interest to report.

Funding/Support and role of the sponsor: None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.02.026.

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10.8. Appendix 8 PREFS Checklist

Table S2 PREFS checklist for assessing quality of preference assessment reporting in the manuscripts included in the review

Question	Answer	
	No/not clear	**Yes**
Purpose: Is the purpose of the study in relation to preferences clearly stated?	The purpose/research question/objectives/ aim does not mention preference, but may mention satisfaction, quality of life, ratings, acceptance	Any reference in the research question/objectives/ aim to preference, utility/disutility, willingness to pay, importance, priorities, goals, revealed preference (eg, choice to continue)
Respondents: Are the responders similar to the nonresponders?	Evidence of significant differences OR No assessment of the difference between responders and nonresponders OR Responders are compared only to a target population rather than nonresponders	Any evidence that the responders do not differ significantly from the nonresponders
Explanation: Are methods of assessing preferences clearly explained?	The question(s) or response options are not clear	The actual preference question is reported in the text or an appendix, or if it is referenced and available elsewhere, and if it is clear what response options were available to respondents, even if the mode of the question (eg, written, oral, online) is not clear OR For studies with multiple questions relating to preferences such as conjoint/discrete choice studies, it is clear what was presented to respondents and what responses were available
Findings: Were all respondents included in the reported findings and analysis of preference results?	Some responses are excluded from the analysis and the possibility of this introducing systematic bias has not been ruled out OR It is not clear whether all respondents were included in the analysis	All respondents who completed the preference question were included in the analysis OR For studies with multiple questions relating to preferences such as conjoint/discrete choice studies, all respondents who at least partially completed the preference questions were included in the analysis OR If some respondents who at least partially completed the preference questions were excluded from the analysis (eg, non-traders, lexicographic preferences, failed test question, irrational preferences, did not complete) AND there is any evidence that those excluded do not differ significantly from those included
Significance: Were significance tests used to assess the preference results?	The study reports only proportions, counts, graphs, etc	The study reports *P*-values, *P*-value ranges (eg, $P<0.05$), confidence intervals, means with standard deviations or standard errors in relation to the preference results (eg, testing the preference hypotheses or study objectives)

Notes: Table reproduced from Springer and *PharmacoEconomics*, 31, 2013, 877–892, Joy SM, Little E, Maruthur NM, et al. Patient preferences for the treatment of type 2 diabetes: a scoping review, Table 1, Copyright © Springer International Publishing Switzerland 2013, with kind permission from Springer Science and Business Media.[1]

10.9. Appendix 9 Validated Tools included in systematic review

Panel 1:

Overview of Health-Related Quality of Life (HRQoL) outcomes and their related assessment tools.

HRQoL

(i) Control Preferences Scale (306) based on five statements to identify the role patients had in making the decision to go on AS:

a. active role with the urologist

b. a shared or collaborative role with the urologist

c. a passive role where the urologist made the decision.

(ii) RAND 36-Item Short-Form Health survey version 2 (SF36v2) (307)

(iii) University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) (308)

Validated Tool	Purpose
Control Preferences Scale (306)	To identify the role patients had in making the decision to go on AS: a. active role with the urologist b. a shared or collaborative role with the urologist c. a passive role where the urologist made the decision.
RAND 36-Item Short-Form Health survey version 2	A 36-Item index, to determine perceived health-related quality of life

(SF36v2) (307)	
University of California, Los Angeles PC Index (UCLA-PCI) (308)	A 20-item index to assess prostate treatment quality of life

Panel 2: Validated Tools included in systematic review

Overview of anxiety outcomes and their related assessment tools.

Anxiety and decision making

(i) A measure of the ability to handle symptoms using the self-efficacy of PC symptom management Symptom management (SE) scale (309)

(ii) An evaluation of depression and contentment with the Mental Health Index – 5 (MHI-5) (310)

(iii) An evaluation of the positive meaning ascribed to cancer with the Fife Constructed Meaning Scale (CMS)(311)

(iv) A measure of illness uncertainty using the Mishel Uncertainty in Illness scale (MUIS)(312)

(v) An evaluation of anxiety using the Memorial Anxiety PC (MAX-PC)(313).

(vi) Five decision- making scales: decisional regret, decision satisfaction, and three aspects of decisional conflict (314-316).

(vii) 11 point, analogue distress thermometer (317) which specifically measures psychological burden in oncology patients.

(viii) Sentiment index (317) to evaluate written text, assigning a numerical value based upon an assessment of positive, negative, or neutral influences

Patient trust in physician scale (318) to rate how much they trusted the physician

Validated Tool	Purpose
Symptom management (SE) scale (309)	A measure of the ability to handle symptoms using the self-efficacy of PC symptom management
Mental Health Index – 5 (MHI-5) (310)	An evaluation of depression and contentment
Fife Constructed Meaning Scale (CMS) (311)	An evaluation of the positive meaning ascribed to cancer
Mishel Uncertainty in Illness scale (MUIS) (312)	A measure of illness uncertainty
Memorial Anxiety PC (MAX-PC) (313)	An evaluation of anxiety
Analogue distress thermometer (317)	11 point, which specifically measures psychological burden in oncology patients.
Sentiment index (317)	To evaluate written text, assigning a numerical value based upon an assessment of positive, negative, or neutral influences
Patient trust in physician scale (318)	To rate how much they trusted the physician
Other in self scale (IOS) (319)	A single-item, pictorial measure of closeness, demonstrated alternate-form and test–retest reliability; convergent validity with the Relationship Closeness Inventory
Five decision-making scales: (314-316).	Decisional regret, decision satisfaction, and three aspects of decisional conflict
Participatory Decision Making (PDM) Scale (320)	3- items, asking patients to rate the physicians' propensity to: 1) involve them in treatment decisions; 2) give them a sense of control over medical care; and 3) ask them to take some responsibility

10.10. Appendix 10 Quality Improvement Project Approval

The ROYAL MARSDEN NHS Foundation Trust **Quality Improvement Project (QIP) Form** (v2)	Date Received: Ref: Initials:

QIP Proposal Form

Please complete the proposal section and return it by e-mail attachment to the appropriate Clinical Audit / QA Facilitator for your Department / Unit at least two weeks before the intended CAC meeting.

QIP Title: Improving quality of life and adherence to Active Surveillance (Prostate cancer)	
Branch: Chelsea	
Division / Directorate / Unit: Urology	
Project Contact Name: Netty Kinsella	**Contact No: 07958 783742**
Project Contact Job Title: Uro-Oncology Nurse Consultant	
Supervising Clinician / Manager (if relevant): Yae-Eun Suh / Declan Cahill	
Other RM staff involved:	
Planned Start Date: January 2018	
Estimated Date of report to go to Clinical Audit Committee : 12 months	

Background Information *Reason for QIP* *State of current knowledge / practice* *How will undertaking this QIP improve patient care?* *State references for any data tools being used e.g. questionnaires.*	Prostate cancer (PC) accounts for 400,000 new cancer cases in Europe [1] annually. European guidelines suggest a large proportion of men with localized, low-risk prostate cancer (LRPC) do not require immediate treatment, but can be monitored – an approach known as active surveillance (AS) [2]. This is optimal as this approach significantly reduces the associated morbidity of radical treatments. However, international variation in determinants for safe AS inclusion and follow-up [3] continue to contribute to high AS drop-out rates (up to 38%) in men with no evidence of disease progression [4]. Recent research reported both in the UK population - ProtecT trial [5] and US equivalent [6], physical and psychological morbidity in AS is comparable to that of patients undergoing radical treatment 2 years following AS initiation. It is unsurprising therefore that men on AS drop out and elect to undergo radical treatment. In terms of follow-up, the UK NICE guidance (2014) [7] suggests that the AS monitoring protocol include 3/12 - 6/12 hospital/specialist review using a combination of blood tests, imaging and repeat biopsies, which represents a significant healthcare burden on hospital teams, however, there is no basis in empirical research to support this protocol and therefore these guidelines are often used flexibly [4]. In addition, there is no

guidance on best practice for supportive care strategies whilst men are on AS.

In the UK, specialists advocating AS provide basic information and/or contact details of a clinical nurse specialist as 'usual care' on AS. In comparison patients choosing radical treatment for prostate cancer receive a combination of specialist nurse input, written information and peer group information and support sessions which have been shown to improve outcomes both physically and psychologically [8-10]. Where replicated in the context of AS, these peer group seminars have halved the number of patients dropping out of AS, from 42% to 22% over a 5 year period [11].

With an increasing number of men eligible for and choosing AS (>1500 men are reviewed on AS each year across the 5 RMH clinic sites – Sutton, Chelsea, Kingston, Croydon and Epsom) both the volume of patients and suggested follow-up protocol constitute a substantial long-term healthcare burden to primary, secondary and tertiary care and therefore a supportive care package with a low-impact surveillance footprint is ideal.

A recent published systematic review (Kinsella et al –European Urology March 2018 [12]) identifying specific themes as facilitators and barriers to AS adherence (see the attached figure). However this is yet to be translated into a viable solution to improve quality of life on AS and support long-term follow-up adherence. Although it is beyond the scope of this QiP to influence national policy, local patient consensus would allow us to develop an information and supportive care peer-group seminar to improve both quality of life on AS and AS adherence in our local population.

This QiP includes two phases

(1) Semi-structured interviews with men who have dropped out of Active Surveillance (without evidence of cancer

guidance on best practice for supportive care strategies whilst men are on AS.

In the UK, specialists advocating AS provide basic information and/or contact details of a clinical nurse specialist as 'usual care' on AS. In comparison patients choosing radical treatment for prostate cancer receive a combination of specialist nurse input, written information and peer group information and support sessions which have been shown to improve outcomes both physically and psychologically [8-10]. Where replicated in the context of AS, these peer group seminars have halved the number of patients dropping out of AS, from 42% to 22% over a 5 year period [11].

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This QiP includes two phases

(1) Semi-structured interviews with men who have dropped out of Active Surveillance (without evidence of cancer

The ROYAL MARSDEN
NHS Foundation Trust

Quality Improvement Project (QIP) Form (v2)

Date Received:
Ref:
Initials:

Objectives *Please itemise each objective i.e. list each issue to be evaluated.* *Incorporate SMART – 'Specific, Measurable, Achievable, Realistic, Timely' principles in devising objectives.*	1.Assess the supportive care needs of men on long-term AS. 2. Form consensus statements to be considered in the development of an active surveillance intervention
Methodology *Initial data collection will be carried out between which dates?* *Sample and number of cases to be selected?* *Type of data analysis planned?* *Potential change that will be implemented (these may change throughout the progression of the QIP)* *Plans for reassessment of data* *Plans for data recording over time period – usually a run chart* *Consider the PDSA cycle [plan, do, study, act]*	*Data will be collected prospectively between January 2018-November 2018.* *Patients will be approached in identified clinics (high volume AS clinics), currently run by both Oncology and Urology teams across the different hospital sites.* *Participants to be identified:* *1.Patients who are currently on AS (for >12 months)* *Patients approached in clinic and willing to participate will be offered to complete the survey online during their appointment or sent the survey by email from netty.kinsella@nhs.net. Questionnaires will be returned by email to netty.kinsella@nhs.net and logged.* *Type of analysis: Prioritisation will be used to analyse the data. 2 rounds of questionnaires are anticipated.* *Patients will be invited to a focus group in February 2019 to establish the content and format of the information and supportive care seminar/webinar.*
Statistical Support requested? No – Will be done by myself with support from Cancer and Epi Dept -Kings College London	
Does this QIP have any cost implications for the trust? No	
Equality Impact: Could any service users or staff be disadvantaged or advantaged in relation to this proposal, based on race, gender, age, disability, religion or belief, sexual orientation, gender reassignment, pregnancy/ maternity or marital/civil partnership status?	No
***Form agreed by relevant Unit / Dept Audit Lead** (Signature)	**Date:**

I CONFIRM MY AGREEMENT to complete this project in accordance with trust policies **Signed: Proposer**		**Date:**
Note: *All countersignatures MUST be obtained either electronically or in handwriting *before* submission to the Clinical Audit Committee and a fully countersigned copy submitted to the relevant Clinical Audit Facilitator in electronic or paper format.		

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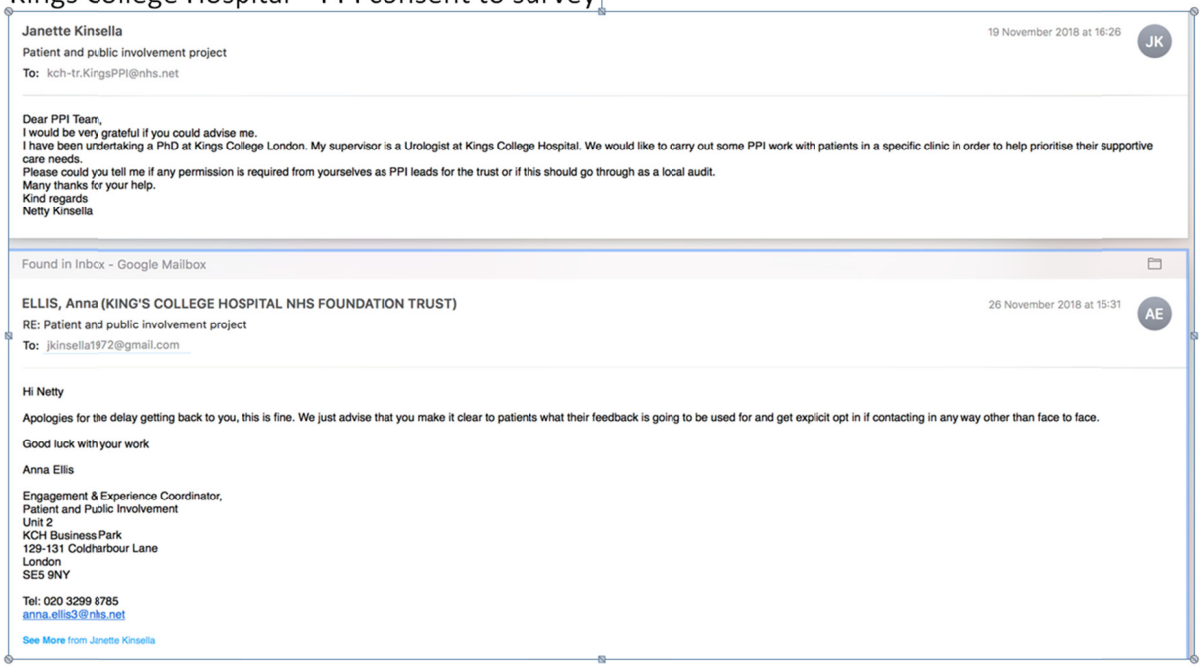
Kings College Hospital – PPI consent to survey



Janette Kinsella 19 November 2018 at 16:26

Patient and public involvement project

To: kch-tr.KirgsPPI@nhs.net

Dear PPI Team,
I would be very grateful if you could advise me.
I have been undertaking a PhD at Kings College London. My supervisor is a Urologist at Kings College Hospital. We would like to carry out some PPI work with patients in a specific clinic in order to help prioritise their supportive care needs.
Please could you tell me if any permission is required from yourselves as PPI leads for the trust or if this should go through as a local audit.
Many thanks for your help.
Kind regards
Netty Kinsella

Found in Inbox - Google Mailbox

ELLIS, Anna (KING'S COLLEGE HOSPITAL NHS FOUNDATION TRUST) 26 November 2018 at 15:31

RE: Patient and public involvement project

To: jkinsella1972@gmail.com

Hi Netty

Apologies for the delay getting back to you, this is fine. We just advise that you make it clear to patients what their feedback is going to be used for and get explicit opt in if contacting in any way other than face to face.

Good luck with your work

Anna Ellis

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See More from Janette Kinsella

10.11. Appendix 11 Patient information Sheet and Letter

Study title: Identifying the barriers and facilitators to long-term active surveillance

You are invited to take part in a service improvement project. Before you decide, it is important for you to understand why the research is being carried out and what we will ask of you. Please read the following information carefully and discuss it with friends or relatives if you wish.

There are two parts to this information sheet:

Part 1

Explains the purpose of this and what your participation in this study will involve.

Part 2

Gives you information about how this study will be conducted.

Please ask if there is anything that is not clear or if you would like more information. We would advise that you take your time to decide if you would like to participate in this study.

Thank you for reading this.

Version [2] 10.01.16

PART 1

What is the purpose of the study?

The purpose of the study is to understand the individual experiences of men on active surveillance for prostate cancer and the barriers and facilitators to long-term adherence to active surveillance.

Why have I been invited to participate?

You have been approached because you dropped out of active surveillance without evidence of your cancer progressing. Your experience would contribute to our understanding of why men drop out of surveillance and opt to undergo treatment. The project is designed to provide a balanced range of views about this.

Do I have to participate in this project?

You can choose to participate in this study. If you do, you have the choice to withdraw from it at any time. Your choice will not affect your treatment in any way.

What will happen if I agree to participate in this study?

If you do agree to participate in this project, Netty Kinsella (Nurse Consultant) will contact you by telephone to confirm that you have not changed your decision. You will be invited for an interview at the hospital which will be arranged on the same day as your clinic appointment where possible. Please let us know if you prefer to have this interview on a different day. The interview should take approximately 30 minutes-1 hour.

During the interview you will be asked to talk about your experience of active surveillance. This interview will be audio-taped. You can say as much or as little as you wish.

Refreshments will be provided during the interview. If you have made a separate journey to attend this interview, your travel expenses on public transport will be reimbursed. You will need to keep your receipts.

If you agree to participate, Netty Kinsella will look at your medical notes for information about your cancer and your treatment. This will help with our interpretation of the information you give us.

What will happen to the audio-tape recordings?

The audio-tape recordings will be written in text and an analysis of the findings will be carried out. The audio-tape recordings will not be used for any other purpose. They will be kept downloaded on the hospitals secure server and only Netty Kinsella will have access to them. We may use anonymous quotes from the interview in the report or future publications.

What are the possible benefits of taking part and how will information be used?

There are no direct personal benefits to the people taking part in this study. However, the findings in this project will help to identify areas that need improvement for future patients in similar situations.

If, after discussing your thoughts during the interview, you feel that there are further issues you would like to be addressed by your hospital team you can contact Netty to discuss and organise this.

What are the possible disadvantages and risks of taking part in the study?

A possible disadvantage of taking part in the study will be the time commitment for the interview.

Some men may find it difficult discussing issues that may arise, for example anxiety, support, family.

If you feel that you would benefit from additional support following the interview, please contact Netty. If appropriate, a referral can be made to your GP or to the psychological support service in the hospital.

Is my participation in this study kept confidential?

Yes. All information which is collected during the course of the project will be kept strictly confidential. Any information arising from the interview will be anonymised. The information will be stored on a secure server (in computer files) which can only be accessed by Netty Kinsella and the research supervisor, Dr Mieke Van Hemelrijck. This complies with the Data Protection Act. Data will be destroyed fifteen years from the end of the study.

On rare occasions, something might be revealed during an interview which must be followed up. If this should happen, Netty will discuss with you what needs to be done.

What will happen to the results of the research study?

The results of this quality improvement project will also be part of a thesis written for Netty Kinsella's doctorate at Kings College London, however, your identity will not be revealed. Findings will be shared within the Trust and submitted for publication in professional and academic journals. Your identity will not be disclosed in any report or publication.

On completion of the project, feedback will be provided via an information sheet for all participants if requested.

Contact details:

For general information please contact Netty Kinsella by telephone on xxx xxx extxxxor e-mail: netty.kinsella@xxxxxxx.nhs.uk.

This completes part 1 of the information sheet; if the information so far has been of interest to you and you are considering participating in it; please continue to read the additional information in part two before making any decision.

PART 2

What if there is a problem?

It is unlikely something will go wrong; however any concern, query or complaint about your experience while participating in the study will be addressed by Netty Kinsella. Alternatively, we can arrange for you to speak to another member of the research team, Dr Mieke VanHemelrijck.

Complaints or concerns that have not been answered to your satisfaction can be referred to the Complaints Manager, following the complaints procedure for the Royal Marsden Hospital. Details of this can be obtained through the Patient Advice & Liaison Service (PALS) department on telephone number: xxx xxx.

What will happen if I do not want to continue in the study?

If at any point you wish to withdraw from the study, you can do so without providing a reason. This is not a problem and the researchers will not use any information already collected, unless you are happy for them to do so. You can discuss this with Netty Withdrawing from the study will not affect the care you receive in any way.

Who has reviewed the study?

This study has been reviewed and approved by the Royal Marsden Hospital Quality Improvement Project committee. .

What should I do now?

If you are interested in participating in the study or have further questions before making a decision, please tell your clinical nurse specialist. Netty is happy to talk to you.

If you decide to participate in this project, you will be contacted with a date to meet Netty. At this appointment, you will be asked to sign the attached consent form.

Contact Information

If you would like any further information about this study please contact Netty Kinsella on xxx xxxextxxxx or your Clinical Nurse Specialist.

Additionally, the Patient Advice and Liaison Service (PALS) is an independent point of contact for all patients who wish to get further advice about the conduct of research studies. The PALS centres can be found at xxxxxxxx. They are opened from 9.30am till 4.00pm Monday till Friday excluding Bank Holidays.

Thank you for taking the time to read this information sheet. I look forward to hearing from you

10.12. Appendix 12 Participant Consent Form

Research project title: Barriers and facilitators to active surveillance for prostate cancer

Research investigator: Netty Kinsella

Research Participants name: XXXXXXXX

Dear……..

Thank you for agreeing to be interviewed as part of the above research project. The interview will take (up to an hour). We don't anticipate that there are any risks associated with your participation, but you have the right to stop the interview or withdraw from the research at any time.

Ethical procedures for academic research undertaken from UK institutions require that interviewees explicitly agree to being interviewed and how the information contained in their interview will be used. This consent form is necessary for us to ensure that you understand the purpose of your involvement and that you agree to the conditions of your participation. Would you therefore read the accompanying information sheet and then sign this form to certify that you approve the following:

- the interview will be recorded and a transcript will be produced
- you will be sent the transcript and given the opportunity to correct any factual errors
- the transcript of the interview will be analysed by (name of the researcher) as research investigator
- access to the interview transcript will be limited to (name of the researcher) and academic colleagues and researchers with whom he might collaborate as part of the research process
- any summary interview content, or direct quotations from the interview, that are made available through academic publication or other academic outlets will be anonymized so that you cannot be identified, and care will be taken to ensure that other information in the interview that could identify yourself is not revealed
- the actual recording will be destroyed

Quotation Agreement:

I also understand that my words may be quoted directly. With regards to being quoted, please initial next to any of the statements that you agree with:

- I wish to review the notes, transcripts, or other data collected during the research pertaining to my participation.
- I agree to be quoted directly.
- I agree to be quoted directly if my name is not published and a made-up name (pseudonym) is used.
- I agree that the researchers may publish documents that contain quotations by me.
- All or part of the content of your interview may be used;
    - In academic papers, policy papers or news articles.
    - On our website and in other media that we may produce such as spoken presentations.
    - On other feedback events.
    - In an archive of the project as noted above

By signing this form I agree that;

1. I am voluntarily taking part in this project. I understand that I don't have to take part, and I can stop the interview at any time;

2. The transcribed interview or extracts from it may be used as described above;

3. I have read the Information sheet;

4. I don't expect to receive any benefit or payment for my participation;

5. I can request a copy of the transcript of my interview and may make edits I feel necessary to ensure the effectiveness of any agreement made about confidentiality;

6. I have been able to ask any questions I might have, and I understand that I am free to contact the researcher with any questions I may have in the future.

Printed Name _____

Participants Signature_____

Date _____

Researchers Signature_____

Date_____

Contact Information:

This project has been reviewed and approved by the Royal Marsden Quality improvement project committee (QIP)

If you have any further questions or concerns about this study, please contact: Netty Kinsella, The Royal Marsden Hospital, London, SW3 6JJ Tel: xxxxxxXextXXXXXX

E-mail: netty.kinsella@rmh.nhs.uk

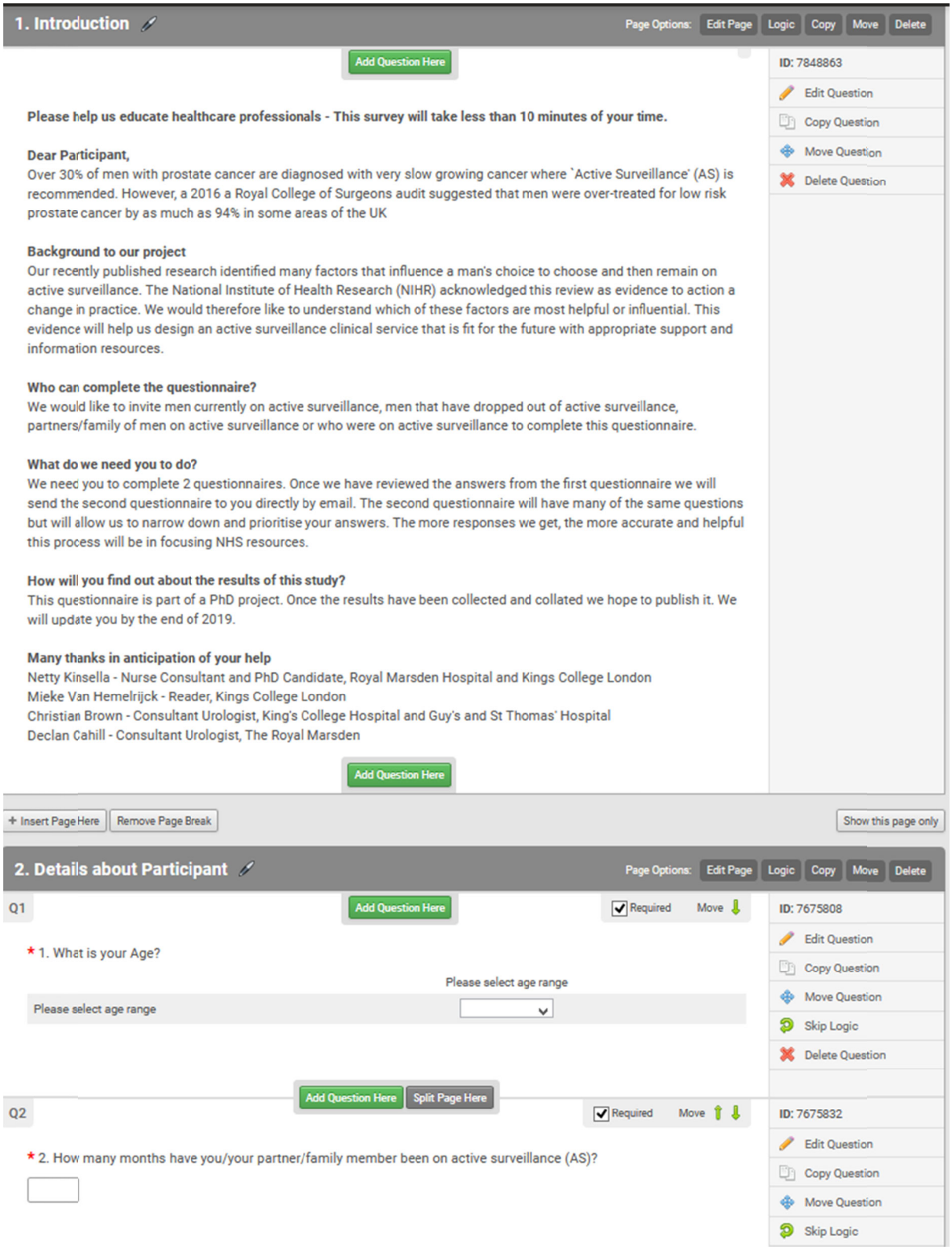
You can also contact (Netty Kinsella) supervisor: Mieke.vanhemelrijck@kcl.ac.uk

10.13. Appendix 13 Pilot interview coding

Pilot interviews

Participant	Transcript	Coder	Coder	Themes
RP	*"...It was one of those gut wrenching moments isn't it when you always think oh I wonder if one day someone is going to say to me "sorry but" and it happened..." "...I just wanted to bury my head, and I did for a while, I only had radiotherapy after my daughter came with me to an appointment..."*	NK	JA	Family pressure Influence of family
RP	*"....There's a wide circle of people with prostate cancer in the bowls club...and some of them have suffered very badly, I wasn't going to regret it....",*	NK	JA	No Treatment regret Regret
CK	*"....When you read things, it says a lot of people with prostate cancer don't know they've got it and die of other things...And you wonder if I hadn't gone to my GP that day, whether I would have, I don't know, maybe not had all this trouble, I might have been ok if they'd just watched it.....".*	NK	JA	Over Treatment regret Regret
RP	*'...you don't know what's going on' because there is no support until after the diagnosis. According to TF, in the waiting room, men were treated 'like a heard of cattle'..."*	NK	JA	Experience of support Lack of support
CK	*"...At diagnosis my scan took three weeks and my biopsy results took four weeks. I almost missed my appointment because the letter arrived the morning of the appointment by which point I was climbing the walls..... It was just the same once I'd started on active surveillance – I couldn't deal with it.... "*	NK	JA	Administrative issues Communication and administration
CK	*"...Although active surveillance was attractive, I just couldn't go through the waiting every 12-18 months. It drove me crazy after the second lot of biopsies so I chose to have surgery.*	NK	JA	Education Communication
	I just think they could sort this out so easily – its customer service. Good service and people are happy..."			Reassurance Education
RP	*"...When [the consultant] recommended AS, [my wife] and I, we made the decision on the spot, like, 'Yes, we'll do that'. I did get cold feet after it, and I rang [nurse] to run through the consultation again, to re-affirm to me that that was why he felt it was the best option. The nurse couldn't have been less interested, she asked why I was so rattled! I'd been on the phone for about 5 minutes when she said she'd have to go now as she had an urgent call to a patient that was in distress. I felt like a nuisance, I just wanted to scream at her that I had cancer too – I was distressed...."*	NK	JA	Communication Education of staff Staff education Prioritising patients (well-being) Supportive care
CK	*"...I was really fortunate, the nurse that I was introduced to spent about an hour with me on the phone the day after my hospital appointment, if she hadn't of phoned I don't know what I would have done. I just didn't understand what the doctor had told me. All I knew was I had cancer and it didn't need treating, I thought that meant that it was incurable!...."*	NK	JA	Communication Clarity of consultation Communication style Consultation style

10.14. Appendix 14 Patient and partner survey's



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* 3. Where do you live (please indicate county (or borough of London) or country if living outside of the UK?

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* 4. Please select the circle that best describes you:

- Partner
- Patient that was previously on active surveillance
- Family member
- Other
- Patient on active surveillance

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* 5. What is your ethnicity?

White

- British
- Irish
- Other

Asian or Asian British

- Indian
- Pakistani
- Bangladeshi
- Any other Asian background

Mixed

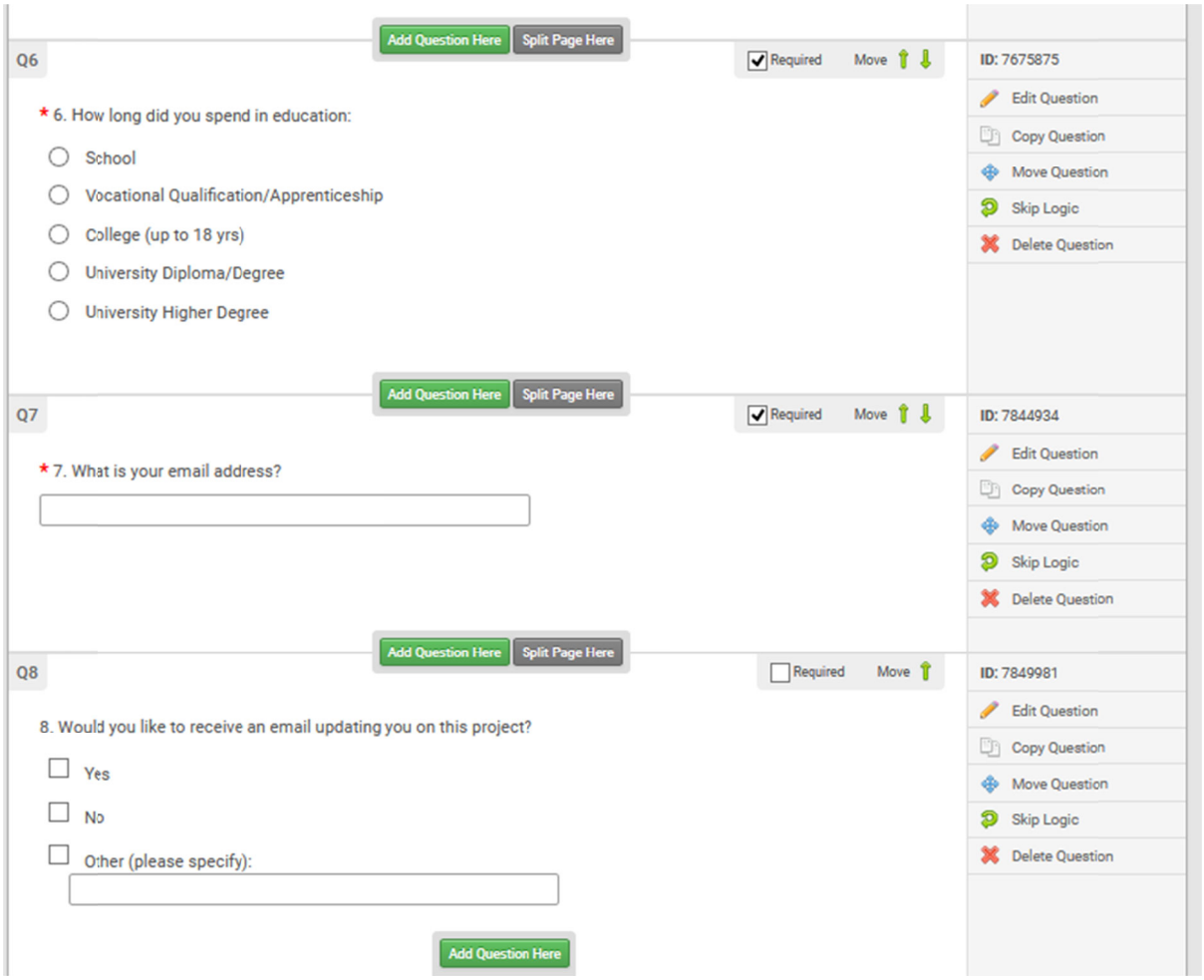
- White and Black Caribbean
- White and black African
- White and Asian
- Any other mixed background

Black or Black British

- Caribbean
- African
- Any other black background

Other Ethnic Group

- Chinese
- Any other Ethnic Group
- I do not wish to disclose my ethnic origin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* 6. How long did you spend in education:
School
Vocational Qualification/Apprenticeship
College (up to 18 yrs)
University Diploma/Degree
University Higher Degree
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* 7. What is your email address?
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8. Would you like to receive an email updating you on this project?
Yes
No
Other (please specify):
Add Question Here


3. Survey Questions
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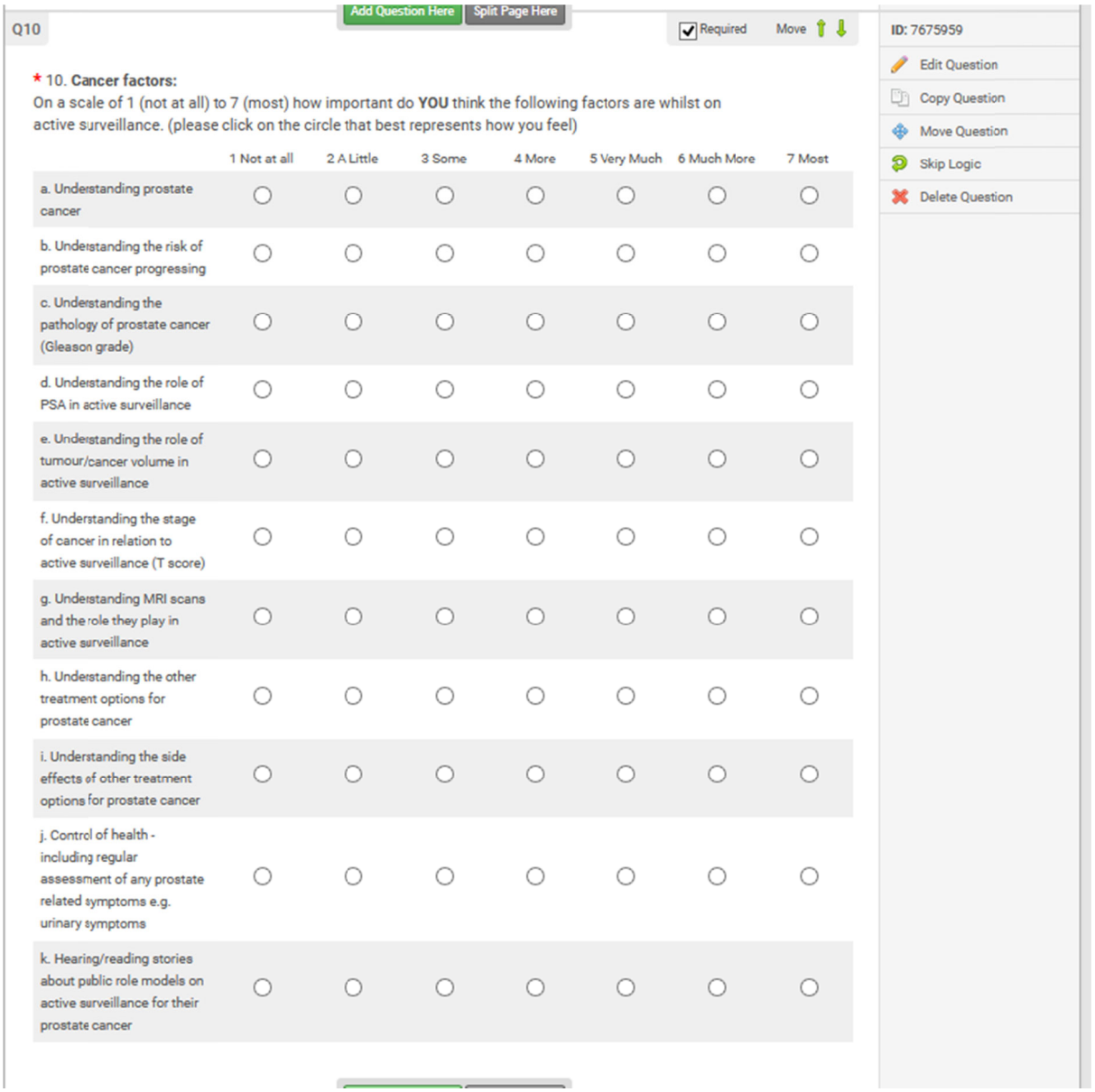
* 9. Patient and Family factors:
On a scale of 1 (not at all) to 7 (most) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)
1 Not At All
2 A Little
3 Some
4 More
5 Very Much
6 Much More
7 Most
a. Feeling involved in decisions about active surveillance e.g. scans and re-biopsy
b. Good physical health whilst on active surveillance
c. Good mental health whilst on active surveillance
d. Access to lifestyle advice from a professional (in relation to prostate cancer)
e. Access to exercise advice from a professional (in relation to prostate cancer)
f. Access to exercise sessions aimed at men with prostate cancer
g. Access to dietary advice from a professional (in relation to prostate cancer)
h. Access to classes in meditation or mindfulness techniques
i. Including partner/family in consultations and cancer decisions
j. Partners/family awareness and knowledge of active surveillance
k. Partners/family acceptance of active surveillance
l. Access to a local support group
m. Recommendation from the hospital clinical team
n. Access to self-management classes
o. Access to reliable sources reporting on the latest research in prostate cancer and active surveillance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* 10. Cancer factors:
On a scale of 1 (not at all) to 7 (most) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)
1 Not at all
2 A Little
3 Some
4 More
5 Very Much
6 Much More
7 Most
a. Understanding prostate cancer
b. Understanding the risk of prostate cancer progressing
c. Understanding the pathology of prostate cancer (Gleason grade)
d. Understanding the role of PSA in active surveillance
e. Understanding the role of tumour/cancer volume in active surveillance
f. Understanding the stage of cancer in relation to active surveillance (T score)
g. Understanding MRI scans and the role they play in active surveillance
h. Understanding the other treatment options for prostate cancer
i. Understanding the side effects of other treatment options for prostate cancer
j. Control of health - including regular assessment of any prostate related symptoms e.g. urinary symptoms
k. Hearing/reading stories about public role models on active surveillance for their prostate cancer

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* 11. **Healthcare provider factors:**
On a scale of 1 (not at all) to 7 (most) how important do **YOU** think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Easy access to the clinical team	○	○	○	○	○	○	○
b. Regular contact with the clinical team (nurse or doctor) via phone	○	○	○	○	○	○	○
c. Regular contact with the clinical team (nurse or doctor) via email	○	○	○	○	○	○	○
d. The clinical team supporting and recommending active surveillance	○	○	○	○	○	○	○
e. Access to reliable information about active surveillance	○	○	○	○	○	○	○
f. Access to up to date research on large active surveillance studies	○	○	○	○	○	○	○
g. Sharing treatment decision making with the clinical team	○	○	○	○	○	○	○
h. Consistently seeing the same clinical team (doctor or nurse)	○	○	○	○	○	○	○

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* 12. **Healthcare organisation factors:**
On a scale of 1 (not at all) to 7(most), how influential do **YOU** think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Agreement on guidelines for safe active surveillance	○	○	○	○	○	○	○
b. The hospital cancelling or moving outpatient appointments	○	○	○	○	○	○	○
c. The hospital cancelling or moving a biopsy date	○	○	○	○	○	○	○
d. The hospital cancelling or moving an MRI scan date	○	○	○	○	○	○	○
e. Difficulty contacting the clinical team	○	○	○	○	○	○	○
f. Difficulty contacting the administrative team	○	○	○	○	○	○	○
g. Being monitored in a cancer centre	○	○	○	○	○	○	○
h. Being monitored by a team/clinician with a special interest in active surveillance	○	○	○	○	○	○	○

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* 13. **Improving support and Information:**
On a scale of 1 (not at all) to 7 (most) how do **YOU** think support and information on active surveillance is best delivered (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Face to face "information and support seminar" given to a group of men on active surveillance (hospital based)	○	○	○	○	○	○	○
b. Face to face 'information and support seminar' given to a group of men on active surveillance (at a local community centre)	○	○	○	○	○	○	○
c. Online website (webinar)	○	○	○	○	○	○	○
d. A health care professional (doctor, nurse, physio etc)	○	○	○	○	○	○	○
e. An expert patient	○	○	○	○	○	○	○
f. An online patient forum/chat room	○	○	○	○	○	○	○
g. A support group for men on active surveillance	○	○	○	○	○	○	○
h. A smartphone app.	○	○	○	○	○	○	○
i. Hospital leaflets or booklets given in clinic	○	○	○	○	○	○	○
j. Charity sponsored leaflets and booklets	○	○	○	○	○	○	○
k. Easy access to community based cancer counsellors	○	○	○	○	○	○	○

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* 14. **Delivering follow-up:**
On a scale of 1 (not at all) to 7 (most) how do **YOU** think follow-up is best delivered where results of blood tests, scans or biopsies are given (please click on the circle that best represents how you feel).

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Face to face appointments	○	○	○	○	○	○	○
b. Telephone appointments	○	○	○	○	○	○	○
c. Email from the clinical team	○	○	○	○	○	○	○
d. Text message from the clinical team	○	○	○	○	○	○	○
e. Skype or FaceTime call from the clinical team	○	○	○	○	○	○	○
f. By a GP	○	○	○	○	○	○	○
g. By a hospital doctor	○	○	○	○	○	○	○
h. By a Specialist Nurse	○	○	○	○	○	○	○
i. In a specialist active surveillance clinic	○	○	○	○	○	○	○

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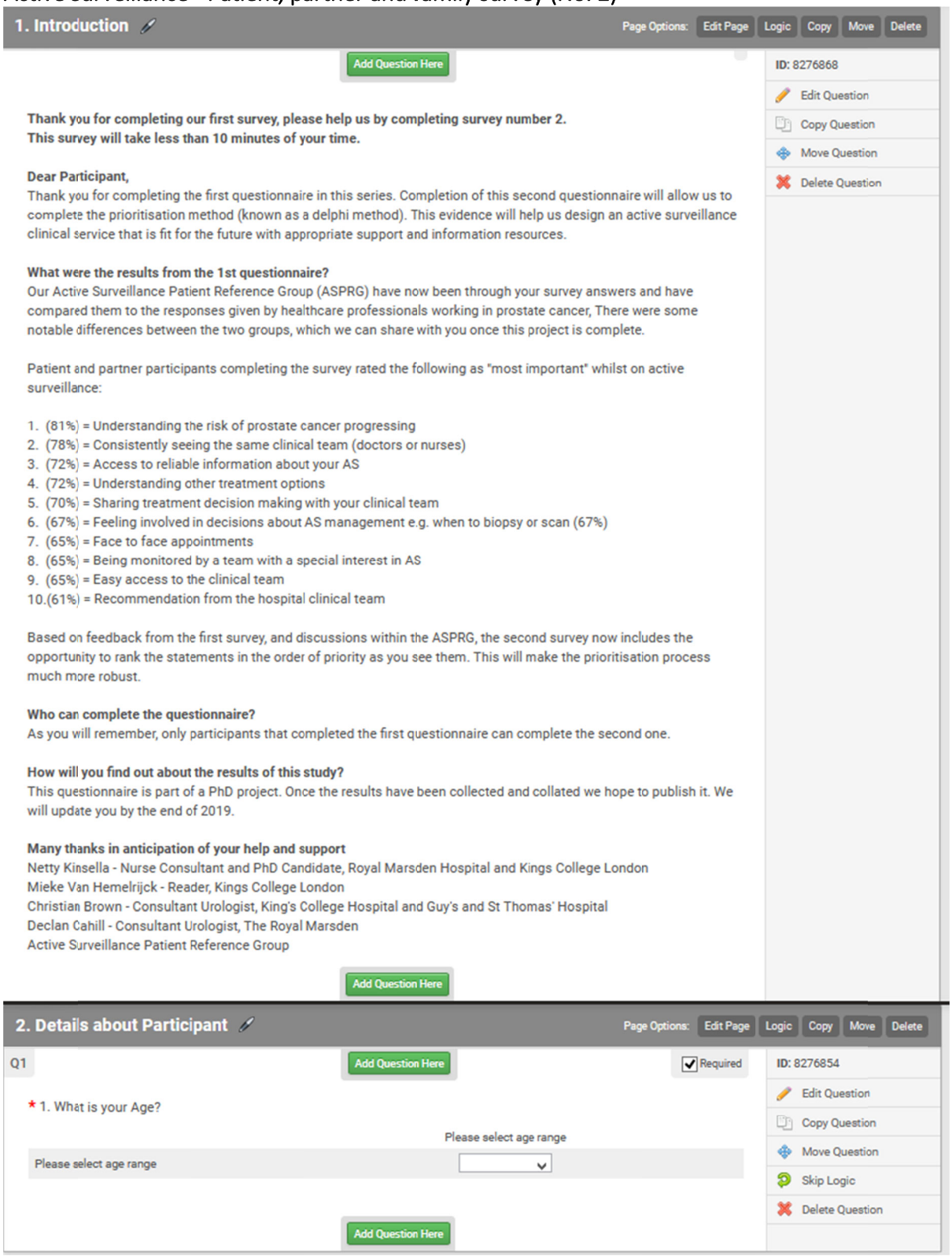
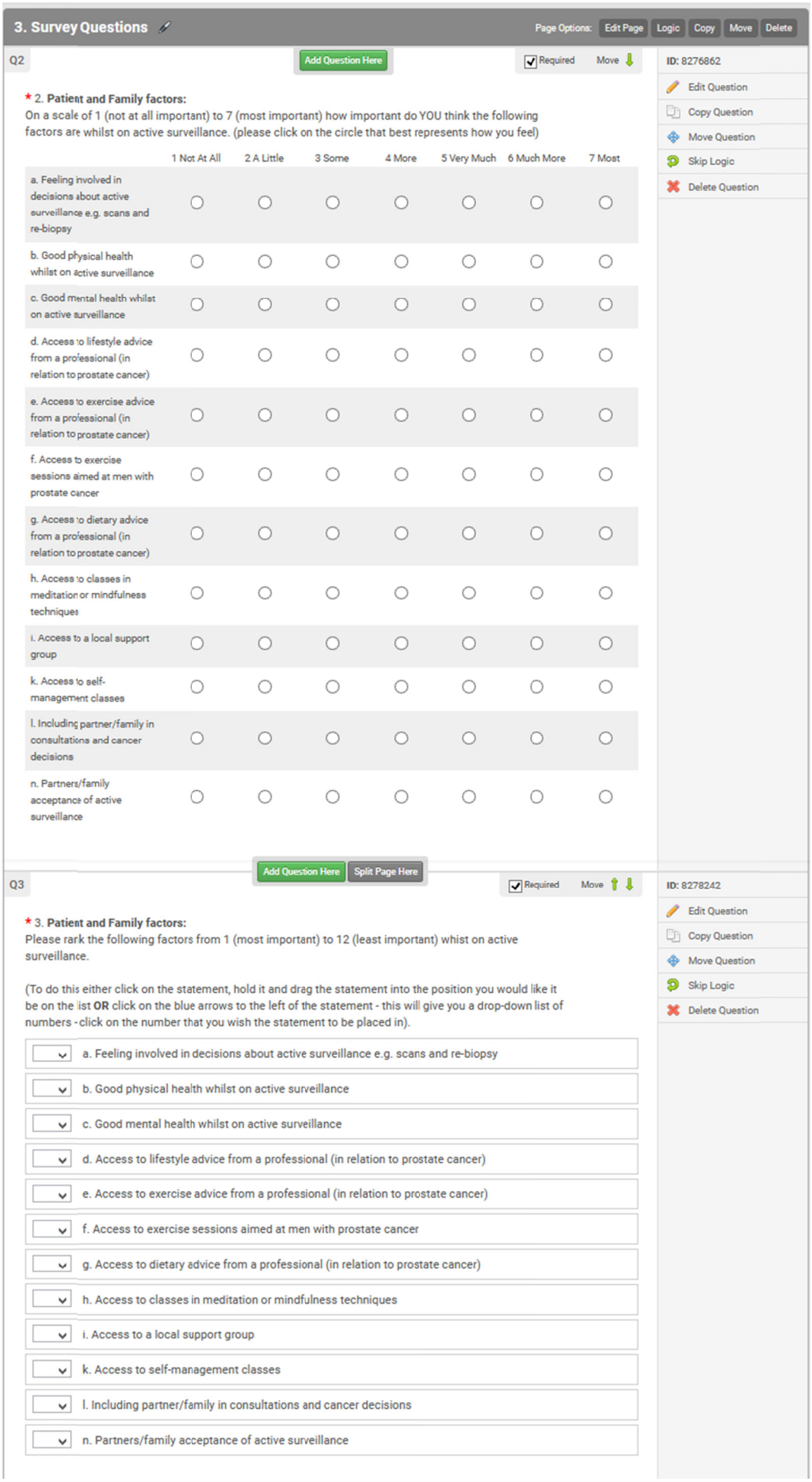
Active surveillance - Patient, partner and family survey (No. 2)





3. Survey Questions

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* 2. **Patient and Family factors:**
On a scale of 1 (not at all important) to 7 (most important) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not At All	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Feeling involved in decisions about active surveillance e.g. scans and re-biopsy	○	○	○	○	○	○	○
b. Good physical health whilst on active surveillance	○	○	○	○	○	○	○
c. Good mental health whilst on active surveillance	○	○	○	○	○	○	○
d. Access to lifestyle advice from a professional (in relation to prostate cancer)	○	○	○	○	○	○	○
e. Access to exercise advice from a professional (in relation to prostate cancer)	○	○	○	○	○	○	○
f. Access to exercise sessions aimed at men with prostate cancer	○	○	○	○	○	○	○
g. Access to dietary advice from a professional (in relation to prostate cancer)	○	○	○	○	○	○	○
h. Access to classes in meditation or mindfulness techniques	○	○	○	○	○	○	○
i. Access to a local support group	○	○	○	○	○	○	○
k. Access to self-management classes	○	○	○	○	○	○	○
l. Including partner/family in consultations and cancer decisions	○	○	○	○	○	○	○
n. Partners/family acceptance of active surveillance	○	○	○	○	○	○	○

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* 3. **Patient and Family factors:**
Please rank the following factors from 1 (most important) to 12 (least important) whist on active surveillance.

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list **OR** click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- a. Feeling involved in decisions about active surveillance e.g. scans and re-biopsy
- b. Good physical health whilst on active surveillance
- c. Good mental health whilst on active surveillance
- d. Access to lifestyle advice from a professional (in relation to prostate cancer)
- e. Access to exercise advice from a professional (in relation to prostate cancer)
- f. Access to exercise sessions aimed at men with prostate cancer
- g. Access to dietary advice from a professional (in relation to prostate cancer)
- h. Access to classes in meditation or mindfulness techniques
- i. Access to a local support group
- k. Access to self-management classes
- l. Including partner/family in consultations and cancer decisions
- n. Partners/family acceptance of active surveillance

Q4

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* 4. **Cancer factors:**
On a scale of 1 (not at all important) to 7 (most important) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Understanding prostate cancer	○	○	○	○	○	○	○
b. Understanding the risk of prostate cancer progressing	○	○	○	○	○	○	○
c. Understanding the pathology of prostate cancer (Gleason grade)	○	○	○	○	○	○	○
d. Understanding the role of PSA in active surveillance	○	○	○	○	○	○	○
e. Understanding the role of tumour/cancer volume in active surveillance	○	○	○	○	○	○	○
f. Understanding the stage of cancer in relation to active surveillance (T score)	○	○	○	○	○	○	○
g. Understanding MRI scans and the role they play in active surveillance	○	○	○	○	○	○	○
h. Understanding the other treatment options for prostate cancer	○	○	○	○	○	○	○
i. Understanding the side effects of other treatment options for prostate cancer	○	○	○	○	○	○	○
j. Control of health - including regular assessment of any prostate related symptoms e.g. urinary symptoms	○	○	○	○	○	○	○

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Q5

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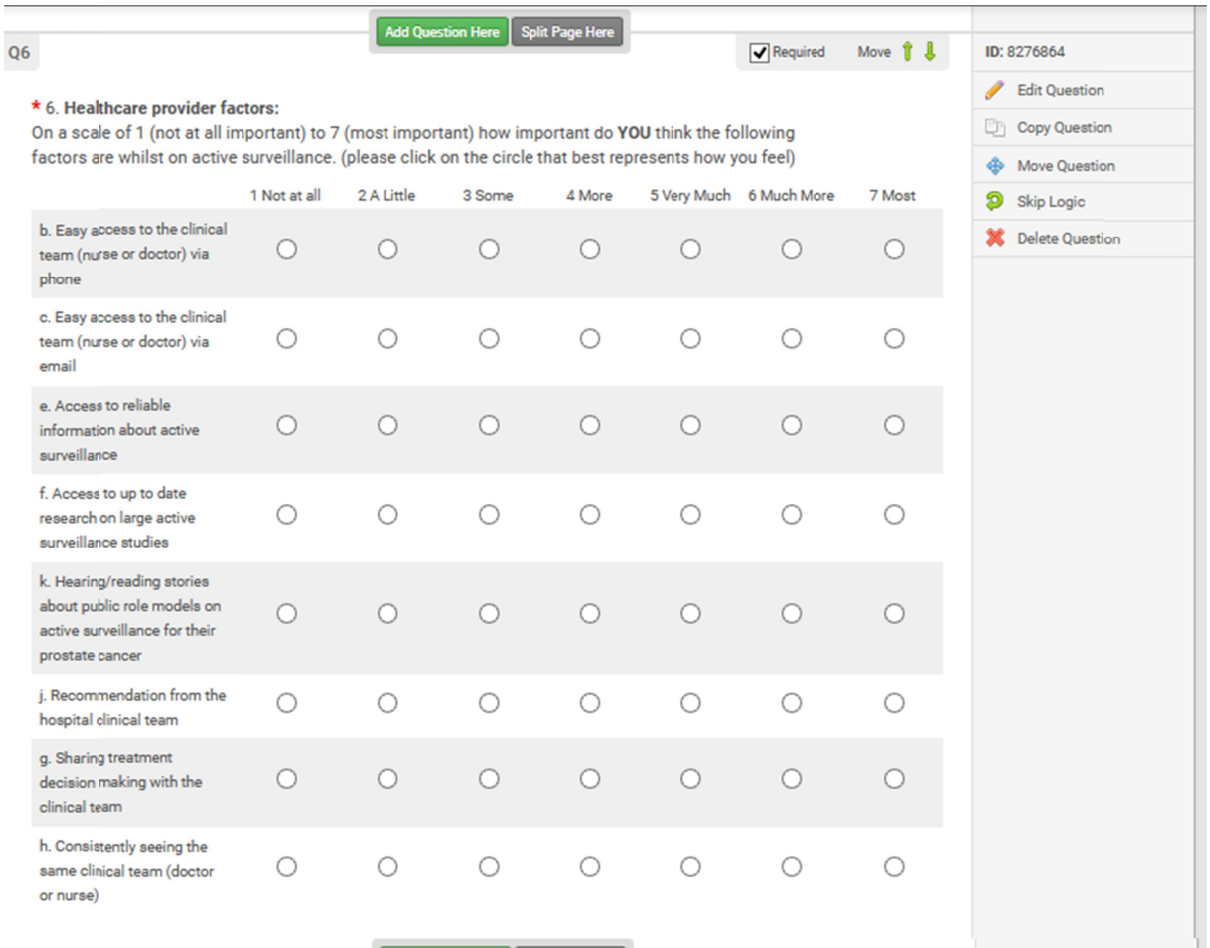
* 5. **Cancer factors:**
Please rank the following factors from 1 (most important) to 10 (least important) whist on active surveillance.

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list **OR** click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- [ ] a. Understanding prostate cancer
- [ ] b. Understanding the risk of prostate cancer progressing
- [ ] c. Understanding the pathology of prostate cancer (Gleason grade)
- [ ] d. Understanding the role of PSA in active surveillance
- [ ] e. Understanding the role of tumour/cancer volume in active surveillance
- [ ] f. Understanding the stage of cancer in relation to active surveillance (T score)
- [ ] g. Understanding MRI scans and the role they play in active surveillance
- [ ] h. Understanding the other treatment options for prostate cancer
- [ ] i. Understanding the side effects of other treatment options for prostate cancer
- [ ] j. Control of health - including regular assessment of any prostate related symptoms e.g. urinary symptoms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Q6
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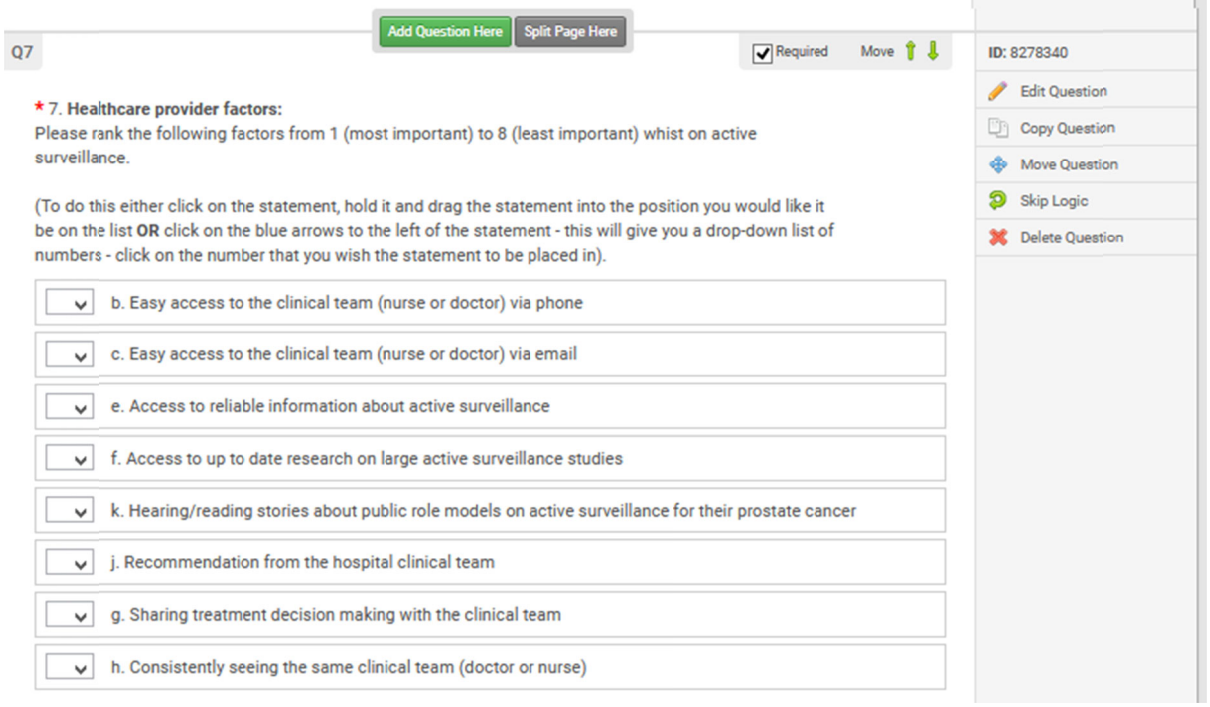
* 6. Healthcare provider factors:
On a scale of 1 (not at all important) to 7 (most important) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)
1 Not at all
2 A Little
3 Some
4 More
5 Very Much
6 Much More
7 Most
b. Easy access to the clinical team (nurse or doctor) via phone
c. Easy access to the clinical team (nurse or doctor) via email
e. Access to reliable information about active surveillance
f. Access to up to date research on large active surveillance studies
k. Hearing/reading stories about public role models on active surveillance for their prostate cancer
j. Recommendation from the hospital clinical team
g. Sharing treatment decision making with the clinical team
h. Consistently seeing the same clinical team (doctor or nurse)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Q7
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* 7. Healthcare provider factors:
Please rank the following factors from 1 (most important) to 8 (least important) whist on active surveillance.
(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list OR click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).
b. Easy access to the clinical team (nurse or doctor) via phone
c. Easy access to the clinical team (nurse or doctor) via email
e. Access to reliable information about active surveillance
f. Access to up to date research on large active surveillance studies
k. Hearing/reading stories about public role models on active surveillance for their prostate cancer
j. Recommendation from the hospital clinical team
g. Sharing treatment decision making with the clinical team
h. Consistently seeing the same clinical team (doctor or nurse)

Q8

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* 8. **Healthcare organisation factors:**
On a scale of 1 (not at all important) to 7 (most important) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A little	3 Some	4 More	5 Very much	6 Much more	7 Most
a. National guidelines for safe active surveillance	○	○	○	○	○	○	○
b. The hospital cancelling or moving outpatient appointments	○	○	○	○	○	○	○
c. The hospital cancelling or moving a biopsy date	○	○	○	○	○	○	○
d. The hospital cancelling or moving an MRI scan date	○	○	○	○	○	○	○
f. Difficulty contacting the administrative team	○	○	○	○	○	○	○
g. Being monitored in a cancer centre	○	○	○	○	○	○	○

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Q9

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* 9. **Healthcare organisation factors:**
Please rank the following factors from 1 (most important) to 6 (least important) whist on active surveillance.

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list OR click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- [ ] a. National guidelines for safe active surveillance
- [ ] b. The hospital cancelling or moving outpatient appointments
- [ ] c. The hospital cancelling or moving a biopsy date
- [ ] d. The hospital cancelling or moving an MRI scan date
- [ ] f. Difficulty contacting the administrative team
- [ ] g. Being monitored in a cancer centre

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Q10

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* 10. **Improving support and Information:**
On a scale of 1 (not at all effective) to 7 (most effective) how do **YOU** think support and information on active surveillance is most effectively delivered (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Face to face "information and support seminar" given to a group of men on active surveillance (hospital based)	○	○	○	○	○	○	○
b. Face to face 'information and support seminar' given to a group of men on active surveillance (at a local community centre)	○	○	○	○	○	○	○
c. Online website (webinar)	○	○	○	○	○	○	○
d. A health care professional (doctor, nurse, physio etc)	○	○	○	○	○	○	○
e. An expert patient	○	○	○	○	○	○	○
f. An online patient forum/chat room	○	○	○	○	○	○	○
g. A support group for men on active surveillance	○	○	○	○	○	○	○
h. A smartphone app.	○	○	○	○	○	○	○
i. Hospital leaflets or booklets	○	○	○	○	○	○	○
j. Charity sponsored leaflets and booklets	○	○	○	○	○	○	○

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Q11 — Required — Move

ID: 8278349

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* 11. **Improving support and Information:**
Please rank the following ways of receiving information about active surveillance from 1 (best option) to 10 (least favourable option).

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list OR click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- a. Face to face "information and support seminar" given to a group of men on active surveillance (hospital based)
- b. Face to face 'information and support seminar' given to a group of men on active surveillance (at a local community centre)
- c. Online website (webinar)
- d. A health care professional (doctor, nurse, physio etc)
- e. An expert patient
- f. An online patient forum/chat room
- g. A support group for men on active surveillance
- h. A smartphone app.
- i. Hospital leaflets or booklets
- j. Charity sponsored leaflets and booklets

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Q12 — Required — Move

ID: 8276867

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* 12. **Delivering follow-up:**
On a scale of 1 (strongly disagree) to 7 (Strongly agree) how do **YOU** think follow-up should be delivered where results of blood tests, scans or biopsies are given (please click on the circle that best represents how you feel).

	1 Strongly disagree	2 Disagree	3 More or less disagree	4 Undecided	5 More of less agree	6 Agree	7 Strongly agree
a. Face to face appointments	○	○	○	○	○	○	○
b. Telephone call from the clinical team	○	○	○	○	○	○	○
c. Email from the clinical team	○	○	○	○	○	○	○
d. Text message from the clinical team	○	○	○	○	○	○	○
e. Skype or FaceTime call from the clinical team	○	○	○	○	○	○	○
f. I should be offered my preferred contact method	○	○	○	○	○	○	○

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Q13 — Required — Move

ID: 8278374

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* 13. **Delivering follow-up:**
Please rank the following options for method of contact with active surveillance results from 1 (best option) to 6 (least favourable option).

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list OR click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- a. Face to face appointments
- b. Telephone call from the clinical team
- c. Email from the clinical team
- d. Text message from the clinical team
- e. Skype or FaceTime call from the clinical team
- f. I should be offered my preferred contact method

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Q14 — Required — Move

ID: 8277950

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* 14. **Delivering follow-up:**
On a scale of 1 (strongly disagree) to 7 (Strongly agree) how do **YOU** think follow-up is best delivered where results of blood tests, scans or biopsies are given (please click on the circle that best represents how you feel).

	1 Strongly disagree	2 Disagree	3 More or less disagree	4 Undecided	5 More or less agree	6 Agree	7 Strongly agree
a. In a hospital based specialist clinic staffed by clinicians with a special interest in active surveillance/prostate cancer	○	○	○	○	○	○	○
b. In a hospital based general urology or oncology clinic	○	○	○	○	○	○	○
c. In a GP clinic (who has a special interest in prostate cancer)	○	○	○	○	○	○	○
d. By your own GP	○	○	○	○	○	○	○

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Q15 — Required — Move

ID: 8278376

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* 15. **Delivering follow-up:**
Please rank the following methods of active surveillance monitoring from 1 (best) to 4 (least favourable) option.

(To do this either click on the statement, hold it and drag the statement into the position you would like it be on the list **OR** click on the blue arrows to the left of the statement - this will give you a drop-down list of numbers - click on the number that you wish the statement to be placed in).

- [ ] a. In a hospital based specialist clinic staffed by clinicians with a special interest in active surveillance/prostate cancer
- [ ] b. In a hospital based general urology or oncology clinic
- [ ] c. In your own GP's clinic
- [ ] d. In a GP's clinic (with a special interest in prostate cancer)

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Q16 — Required — Move

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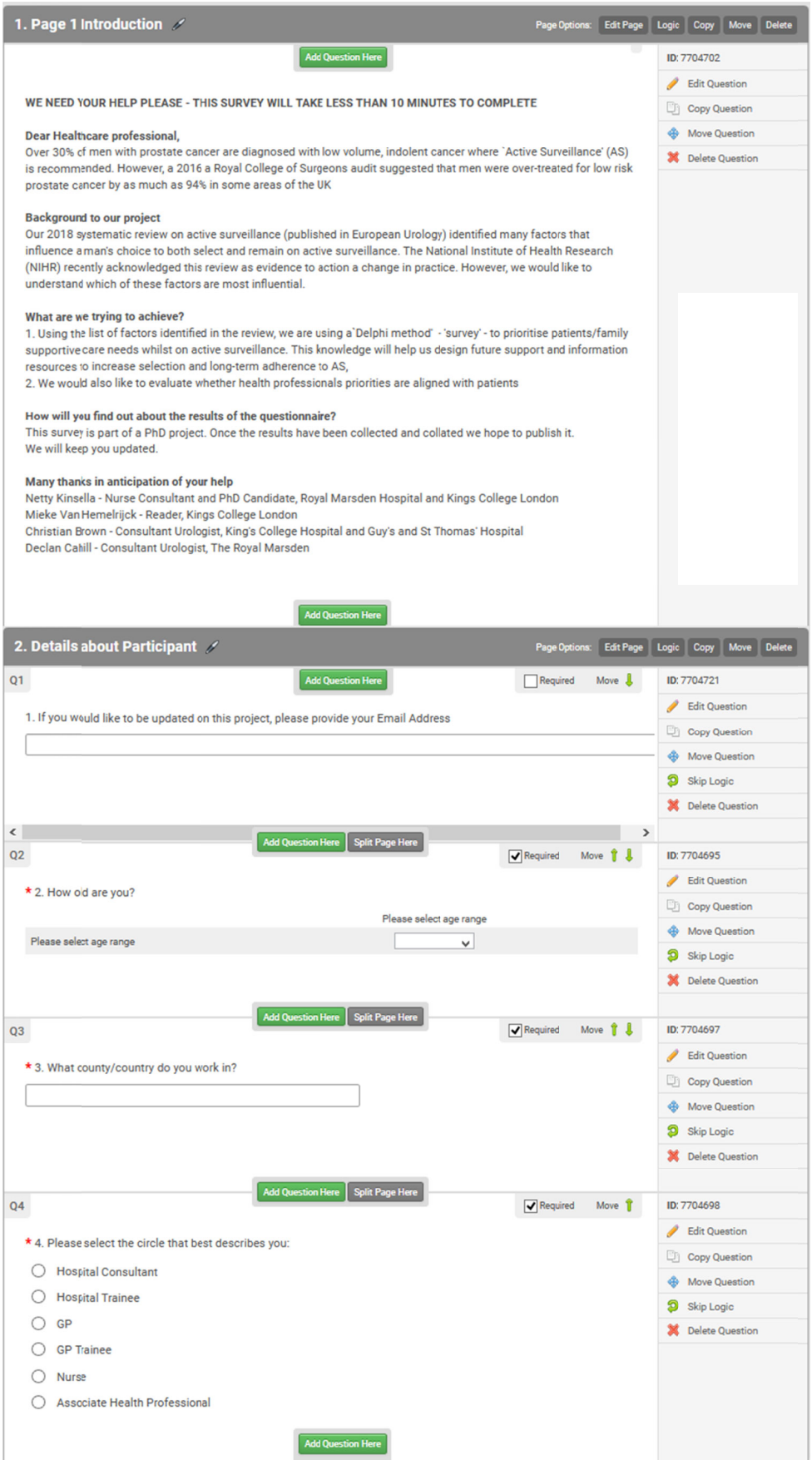
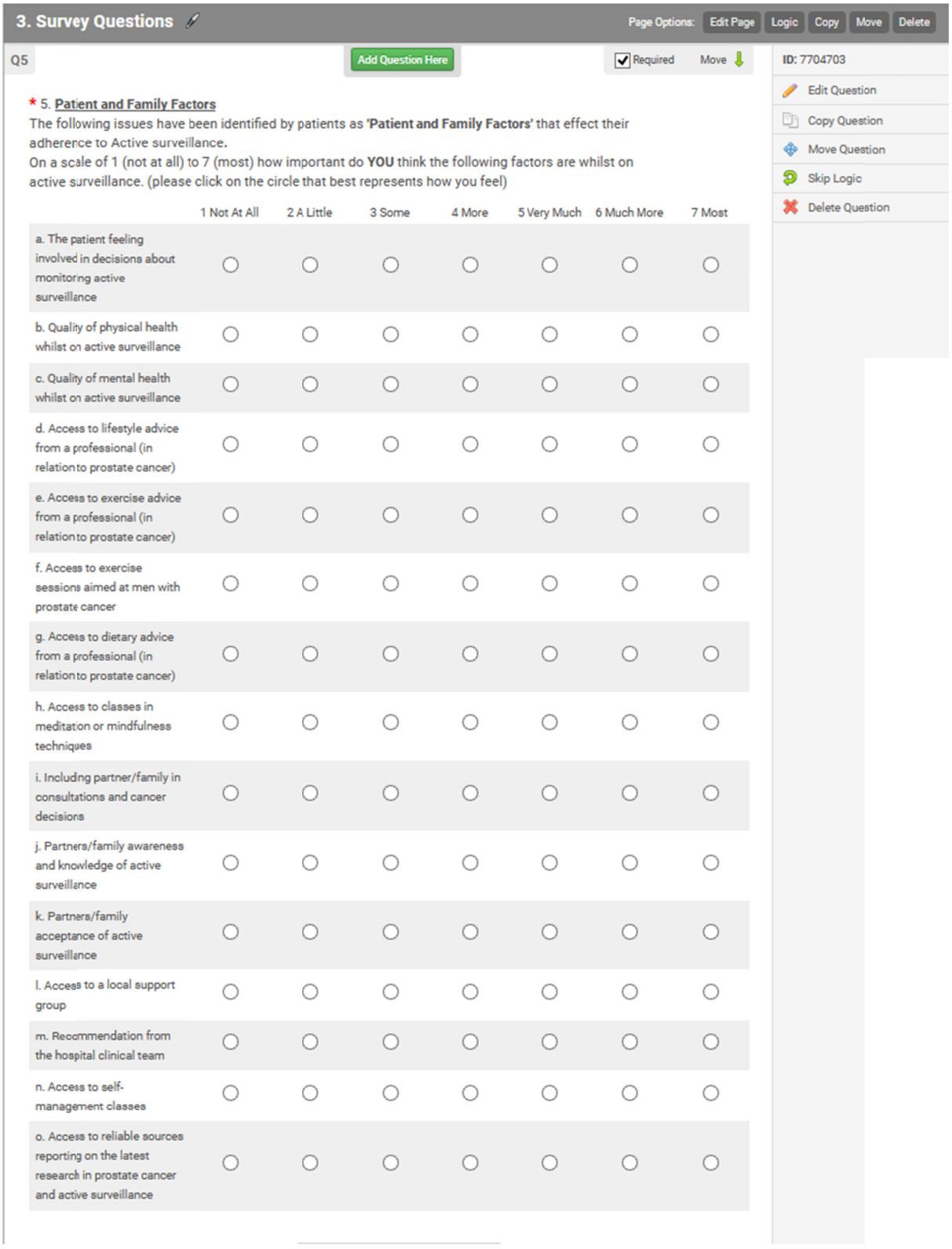
16. If you have any further comments that you would like us to consider please feel free to include them in this free text box.

10.15. Appendix 14 HCP survey




3. Survey Questions
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Q5
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* 5. Patient and Family Factors
The following issues have been identified by patients as 'Patient and Family Factors' that effect their adherence to Active surveillance.
On a scale of 1 (not at all) to 7 (most) how important do YOU think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)
1 Not At All
2 A Little
3 Some
4 More
5 Very Much
6 Much More
7 Most
a. The patient feeling involved in decisions about monitoring active surveillance
b. Quality of physical health whilst on active surveillance
c. Quality of mental health whilst on active surveillance
d. Access to lifestyle advice from a professional (in relation to prostate cancer)
e. Access to exercise advice from a professional (in relation to prostate cancer)
f. Access to exercise sessions aimed at men with prostate cancer
g. Access to dietary advice from a professional (in relation to prostate cancer)
h. Access to classes in meditation or mindfulness techniques
i. Including partner/family in consultations and cancer decisions
j. Partners/family awareness and knowledge of active surveillance
k. Partners/family acceptance of active surveillance
l. Access to a local support group
m. Recommendation from the hospital clinical team
n. Access to self-management classes
o. Access to reliable sources reporting on the latest research in prostate cancer and active surveillance

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Q6

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* 6. **Cancer Factors**

The following issues have been identified by patients as **'Cancer factors'** that effect their adherence to Active surveillance

On a scale of 1 (not at all) to 7 (most) how important do **YOU** think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Understanding prostate cancer	○	○	○	○	○	○	○
b. Understanding the risk of prostate cancer progressing	○	○	○	○	○	○	○
c. Understanding the pathology of prostate cancer (Gleason grade)	○	○	○	○	○	○	○
d. Understanding the role of PSA in active surveillance	○	○	○	○	○	○	○
e. Understanding the role of tumour volume in active surveillance	○	○	○	○	○	○	○
f. Understanding the stage of cancer in relation to active surveillance (T scores)	○	○	○	○	○	○	○
g. Understanding MRI scans and the role they play in active surveillance	○	○	○	○	○	○	○
h. Understanding the other treatment options for low-intermediate risk prostate cancer	○	○	○	○	○	○	○
i. Understanding the side effects of other treatment options for prostate cancer	○	○	○	○	○	○	○
j. Control of health - including regular assessment of any prostate related symptoms e.g. urinary symptoms	○	○	○	○	○	○	○
k. Hearing/reading stories about public role models on active surveillance for their prostate cancer	○	○	○	○	○	○	○

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Q7

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ID: 7704705

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* 7. **Healthcare provider factors:**

The following issues have been identified by patients as **'Healthcare provider factors'** that effect their adherence to Active surveillance

On a scale of 1 (not at all) to 7(most) how important do **YOU** think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Easy access to the clinical team	○	○	○	○	○	○	○
b. Regular contact with the clinical team (nurse or doctor) via phone	○	○	○	○	○	○	○
c. Regular contact with the clinical team (nurse or doctor) via email	○	○	○	○	○	○	○
d. The clinical team supporting and recommending active surveillance	○	○	○	○	○	○	○
e. Access to reliable information about active surveillance	○	○	○	○	○	○	○
f. Access to up to date research on large active surveillance studies	○	○	○	○	○	○	○
g. Sharing treatment decision making with the clinical team	○	○	○	○	○	○	○
h. Consistently seeing the same clinical team (doctor or nurse)	○	○	○	○	○	○	○

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Q8

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* 8. **Healthcare organisation factors:**

The following issues have been identified by patients as '**Healthcare organisation factors**' that effect their adherence to Active surveillance

On a scale of 1 (not at all) to 7(most), how influential do **YOU** think the following factors are whilst on active surveillance. (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Clear National or Local guidelines for safe active surveillance	○	○	○	○	○	○	○
b. The hospital cancelling or moving outpatient appointments	○	○	○	○	○	○	○
c. The hospital cancelling or moving a biopsy date	○	○	○	○	○	○	○
d. The hospital cancelling or moving an MRI scan date	○	○	○	○	○	○	○
e. Difficulty contacting the clinical team	○	○	○	○	○	○	○
f. Difficulty contacting the administrative team	○	○	○	○	○	○	○
g. Being monitored in a cancer centre	○	○	○	○	○	○	○
h. Being monitored by a team/clinician with a special interest in active surveillance	○	○	○	○	○	○	○

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Q9

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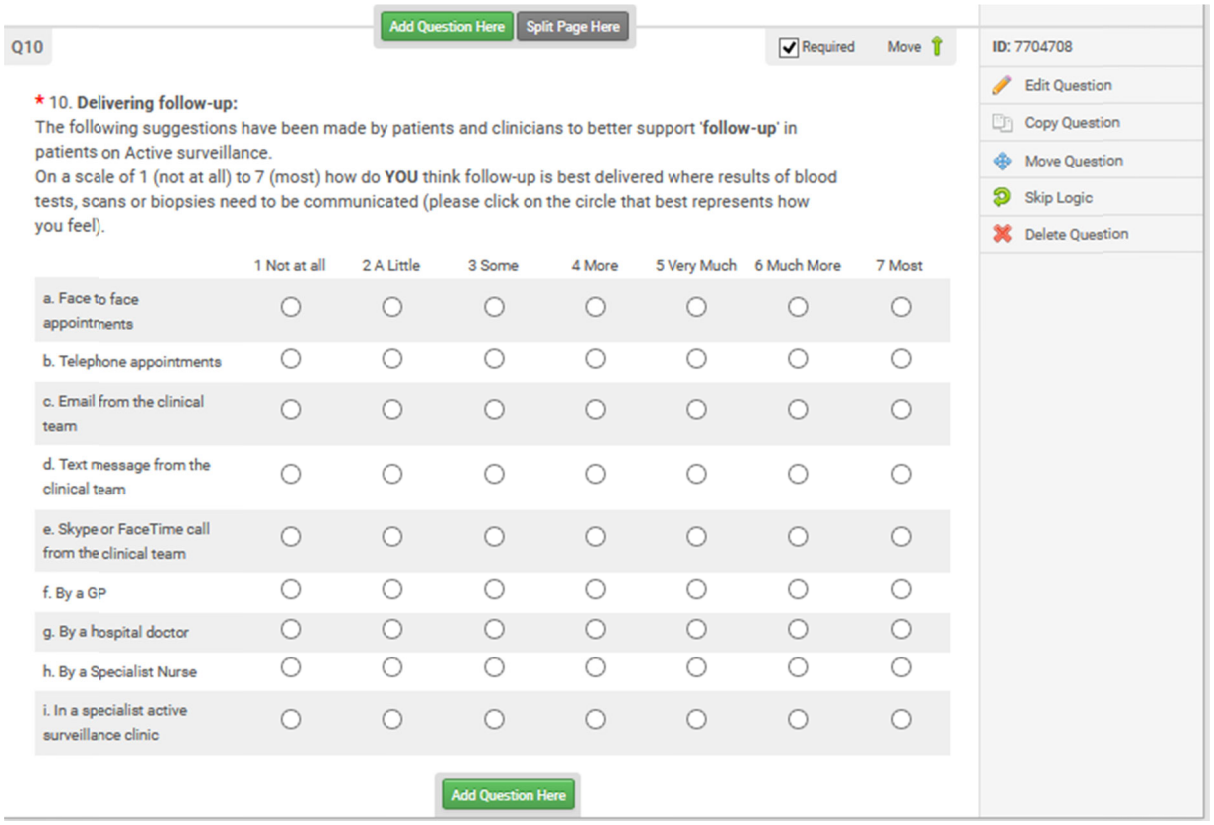
* 9. **Support and Information:**

The following suggestions have been made by patients and clinicians to better '**Support and inform**' patients on Active surveillance

On a scale of 1 (not at all) to 7 (most) how do **YOU** think support and information on active surveillance is best delivered (please click on the circle that best represents how you feel)

	1 Not at all	2 A Little	3 Some	4 More	5 Very Much	6 Much More	7 Most
a. Face to face "information and support seminar" given to a group of men on active surveillance (hospital based)	○	○	○	○	○	○	○
b. Face to face 'information and support seminar' given to a group of men on active surveillance (at a local community centre)	○	○	○	○	○	○	○
c. Online website (webinar)	○	○	○	○	○	○	○
d. A health care professional (doctor, nurse, physio etc)	○	○	○	○	○	○	○
e. An expert patient	○	○	○	○	○	○	○
f. An online patient forum/chat room	○	○	○	○	○	○	○
g. A support group for men on Active Surveillance	○	○	○	○	○	○	○
h. A smartphone app.	○	○	○	○	○	○	○
i. Hospital leaflets or booklets given in clinic	○	○	○	○	○	○	○
j. Charity sponsored leaflets and booklets	○	○	○	○	○	○	○
k. Easy access to community based cancer counsellors	○	○	○	○	○	○	○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Q10
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* 10. Delivering follow-up:
The following suggestions have been made by patients and clinicians to better support 'follow-up' in patients on Active surveillance.
On a scale of 1 (not at all) to 7 (most) how do YOU think follow-up is best delivered where results of blood tests, scans or biopsies need to be communicated (please click on the circle that best represents how you feel).
1 Not at all
2 A Little
3 Some
4 More
5 Very Much
6 Much More
7 Most
a. Face to face appointments
b. Telephone appointments
c. Email from the clinical team
d. Text message from the clinical team
e. Skype or FaceTime call from the clinical team
f. By a GP
g. By a hospital doctor
h. By a Specialist Nurse
i. In a specialist active surveillance clinic
Add Question Here